DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIVIRAL DRUGS ADVISORY COMMITTEE

BLA 125283 motavizumab

Wednesday, June 2, 2010

8 o'clock a.m.

Hilton Washington DC/Silver Spring
Maryland Ballroom
8727 Colesville Road
Silver Spring, MD

C O N T E N T S

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Paul T. Tran, R.Ph., Designated Federal Official

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William Tauber, M.D.
Alan Shapiro, M.D
Jules O'Rear, Ph.D.

P R O C E E D I N G S

Call to Order

DR. HENDRIX: Good morning. I would first like to remind everyone present to please silence your cell phones, Blackberrys and other devices if you have not already done so. I would also like to identify the FDA press contact, Ms. Erica Jefferson. If you are here present, if you will please stand. Okay. So she is not here yet. But the press contact would be Ms. Erica Jefferson.

Call to Order

My name is Craig Hendrix. I am the Acting Chair of the Antiviral Drugs Advisory Committee. I will now call the meeting of the Antiviral Drugs Advisory Committee to order.

We are going to begin by going around the room. I would ask if you would please introduce yourself. We will start first with the FDA and Dr. Edward Cox to my left. Then we will come around the table in a counterclockwise direction.

DR. COX: Good morning. Ed Cox, Director of the Office of Antimicrobial Products, CDER, FDA.

DR. BIRNKRANT: Debra Birnkrant, Director,

Division of Antiviral Products, FDA.

DR. TAUBER: Bill Tauber, Division of Antiviral Products. I am a medical officer.

DR. SHAPIRO: Alan Shapiro, clinical reviewer, Division of Antiviral Products.

DR. O'REAR: Jules O'Rear, Microbiology Team Leader, Antiviral Products.

DR. MURATA: Yoshi Murata, Infectious Diseases, University of Rochester.

DR. ATKINSON: Prescott Atkinson, Allergy/Immunology, UAB.

DR. MALDONADO: Yvonne Maldonado, Department of Pediatrics, Division of Infectious Diseases, Stanford University.

DR. CARGILL: Victoria Cargill, Office of AIDS Research, National Institutes of Health.

DR. HENDRIX: Craig Hendrix, Johns Hopkins, clinical pharmacology.

MR. TRAN: Paul Tran, the DFO for the Antiviral Drug Advisory Committee.

DR. CLAY: Patrick Clay, Kansas City University of Medicine, biosciences.

MS. WALDEN: Angelica Walden, Quality Management, MCG Medical Center.

DR. ELLENBERG: Susan Ellenberg, biostatistics, University of Pennsylvania School of Medicine.

DR. FREEMAN: Alexandra Freeman, Laboratory of Clinical Infectious Diseases at NIAID, NIH.

DR. ROLAND: Michelle Roland, California Department of Public Health Office of AIDS.

DR. GRAHAM: Barney Graham, Vaccine Research Center, NIH.

DR. RALSTON: Shawn Ralston, Division of Inpatient Pediatrics, University of Texas, San Antonio.

DR. HAVENS: Peter Havens, Medical College of Wisconsin and Children's Hospital Wisconsin, pediatric infectious diseases.

DR. STRADER: Doris Strader, Division of Gastroenterology and Hepatology, University of Vermont.

DR. HAGEDORN: Kurt Hagedorn, University of Utah, Division of Gastroenterology/Hepatology, Department of Medicine.

DR. HAVENS: Rick Veltri, Merck Research Laboratories, Industry Representative.

DR. HENDRIX: Thank you you all for the introductions.

For topics such as those being discussed at today's meeting, there are often a variety of opinions some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair and we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government and the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during the breaks or

during lunch.

Thank you.

Mr. Paul Tran will read the Conflict of Interest Statement.

Conflict of Interest Statement

MR. TRAN: Good morning. The Food and Drug Administration is convening today's meeting of the Antiviral Drugs Advisory Committee of the Center for Drug Evaluation and Research under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict-of-interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict-of-interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act is being provided to participants in today's meeting and to the public.

The FDA has determined that members and temporary

voting members of this committee are in compliance with federal ethics and conflict-of-interest laws. Under 18 U.S.C. Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include: investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents

and royalties; and primary employment.

Today's agenda involves discussion of Biologics License Application NDA 125283 for motavizumab manufactured by MedImmune LLC for the prevention of serious lower respiratory-tract disease caused by respiratory syncytial virus, RSV, in children with high risk for RSV disease.

This is a particular-matters meeting during which specific matters related to MedImmune's motavizumab will be discussed.

Based on the agenda and all financial interests reported by the committee members and temporary voting members, no conflict-of-interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the issues being discussed today.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Enrico Veltri is participating in today's meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Veltri's role at this meeting is to represent

industry in general and not any particular company. Dr. Veltri is employed by Merck Research Laboratories.

We would like to remind members and temporary voting members that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they have with any firms at issue.

Thank you.

DR. HENDRIX: Thank you.

We will now proceed with the FDA Opening Remarks from Dr. Debra Birnkrant. I would like to remind public observers at the meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

FDA Opening Remarks

DR. BIRNKRANT: Good morning.

[Slide.]

I would like to welcome everyone to today's advisory committee meeting where we will be discussing MedImmune's biologic licensing application for motavizumab.

Before we get to more scientific aspects of today's discussion, I wanted to mention a few things. At the time that our background document was written, we had not completed our reviews. However, the background document represented our understanding of the data at that time. As of today, the review is continuing. Not all of the inspections of the clinical trials have been completed, but they are scheduled.

I would also like to state that on Sunday we were made aware of an article that appeared in the May 28, 2010 edition of the Washington Business Journal that outlined an incident involving a former MedImmune employee and the product under discussion today.

A civil suit has been filed in the Montgomery County Circuit Court against MedImmune. We don't have information except for what is public and we haven't been able to look into the situation in depth. We wanted to be transparent about the situation and fully disclose what we know at present. We recognize that it needs to be evaluated

further and we will inform the committee of any additional information in the future.

Nonetheless, our purpose today is to present and evaluate the scientific data that was submitted and reviewed to determine if its merits are sufficient to conclude that the benefits of this drug, motavizumab, outweigh its risks.

[Slide.]

Now let's turn to RSV. RSV is an enveloped RNA paramyxovirus lacking neuraminidase and hemaglutten surface proteins. It causes acute respiratory-tract illness in all ages and, in fact, it has been reported that, in adults, morality and morbidity are comparable to Influenza A. However, that is not the subject of today's meeting. We will be focusing on children today. It is the most important cause of bronchiolitis and pneumonia in infants and young children.

[Slide.]

Important characteristics that increase the risk of severe or fatal RSV infection in children include prematurity, cyanotic or complicated congenital heart disease, chronic lung disease of prematurity, and two other factors, immunodeficiency and therapies causing

immunosuppression. We will not be discussing the latter two areas, however.

[Slide.]

Now let's turn to the regulatory history. We will start with palivizumab or Synagis. This is a monoclonal antibody directed against the F protein or fusion protein of RSV. It was initially approved for passive immunoprophylaxis in 1998 at a dose of 15 mg/kg IM every 30 days for approximately five doses during RSV season. It was originally indicated for prevention of RSV in premature infants less than 35 weeks gestation with chronic lung disease of prematurity based on Study 018.

It was subsequently approved for use in children with hemodynamically significant congenital heart disease based on Study 048.

[Slide.]

Motavizumab is also a humanized monoclonal antibody derived from its approved parent monoclonal antibody palivizumab, which I just mentioned. It is also for passive immunoprophylaxis against RSV at the same dose, 15 mg/kg IM. It is also directed against the RSV F protein. However, it differs from palivizumab by 13 amino-acid

residues which may increase binding avidity with enhanced in vitro neutralizing activity relative to palivizumab.

[Slide.]

Let's now look at the regulatory history for motavizumab. It October of 2003, there was an initial dose-finding study in adults. Subsequently, there were four additional phase 1-2 trials conducted. In the fall of 2004, the phase 3 trial, CP110, was initiated.

In May, 2005, there was a formal end-of-phase-2 meeting. MedImmune also enrolled patients with hemodynamically significant congenital heart disease in a separate study, CP124, so not part of the CP110 population. In 2007, a pre-BLA meeting was held.

[Slide.]

The planned original biologics licensing application submission was to contain a single large phase-3 trial comparing motavizumab to palivizumab in Study CP110. The primary endpoint was prevention of RSV hospitalization and the noninferiority margin for the trial CP110 was based on palivizumab trial 018.

However, differences were noted by the 018 population in which palivizumab was studied and CP110 with

respect to hospitalization rates, proportion of subjects with chronic lung disease of prematurity, less then 32 weeks gestational age and the different geographic site selection.

So it was decided to include Native American Study CP117 in the BLA for motavizumab. This was to be used as a supportive study although it was recognized that subjects enrolled in CP117 were healthy, full-term infants previously recognized to be at high risk of serious RSV disease compared to other healthy full-term infants.

[Slide.]

The initial BLA submission was in January of 2008. Our initial action was a complete response letter sent in November, 2008, to MedImmune. The complete response letter is a more consistent and neutral mechanism to convey that FDA cannot approve an application in its present form.

We were unable to complete our review without additional data. MedImmune responded to us in December of 2009 and we are at the Antiviral Advisory Committee Meeting today.

[Slide.]

What types of data did we request in the CR letter? Well, the decision to admit patients was not

performed solely on clinical grounds but could have included the use of local RSV testing. However, upon our review, we determined that it didn't appear that local testing was uniformly applied and could this practice impact hospitalization which would impact the primary endpoint.

Upon our initial review, it appeared as though the study medications appeared to interfere with some licensed local RSV assays and some centrally used real-time RT-PCR results were discordant with the local RSV assay results.

[Slide.]

We requested a chart review for principal Studies 110 and 117 and subjects presenting with respiratory-tract infection. We wanted an assessment of the local test results and the testing methodologies that were used to ascertain if there was interference by the study medications.

[Slide.]

In addition, our CR letter asked for the following. There were an increased number of patient deaths and apparent life-threatening events among the motavizumab recipients compared to palivizumab or placebo. So we needed an explanation for that. There appeared to be an imbalance

in the incidence of specific categories of neurologic adverse events including serious adverse events between motavizumab and palivizumab or placebo.

In the phase 3 studies, testing for anti-motabizumab antibodies was performed at a time when remaining circulating drug was likely to have affected the results.

[Slide.]

Further, there appeared to be a link between the development of anti-drug antibodies and the occurrence of hypersensitivity reactions post dosing.

The applicant submitted a complete response, as I mentioned, in December of 2009. Within that complete response was an additional study in patients with congenital heart disease, Study 124. The complete response that was submitted in December enabled us to continue our review to ultimately be able to make a risk/benefit decision.

[Slide.]

We will have a number of questions for the panel today, and I would like to highlight those for you. We will be asking the panel to comment on the safety profile of motavizumab specifically with respect to the potential for

hypersensitivity reactions including anaphylaxis.

We will be asking the committee whether or not the data adequately support the efficacy of motavizumab for prevention of serious lower respiratory-tract infection in patients at high risk for RSV. And there will be one voting question; given the potential benefits and risks, should motavizumab be licensed for marketing.

Then there is a further delineation of that question; if no, what additional studies should be required and, if yes, are the postmarketing studies needed to provide additional safety or optimized use of the drug.

[Slide.]

So, overall, our meeting goals are, at the end of the day following the presentations and discussion and the questions, can we conclude that the benefits are greater than the risks for motavizumab for the following proposed indication; for the prevention of serious lower respiratory-tract disease caused by RSV in children at high risk of RSV disease.

[Slide.]

I would like to share with you the agenda today. Following my comments, there will be a 90-minute

presentation by MedImmune. This will be followed by a brief period for clarification and questions. We will then take a 15-minute break. This will be followed by the FDA presentation by Dr. Alan Shapiro. Again, we will have another session for clarification and questions. We will take a lunch break at noon for one hour.

There will be an open public hearing if anyone has signed up to speak. Then we will present the committee with the questions.

Thank you very much.

DR. HENDRIX: Thank you, Dr. Birnkrant.

We will now proceed with the sponsor presentations. I would like to remind public observers at the meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria and interest in the sponsor include equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

Applicant Presentation--MedImmune LLC
Regulatory Affairs, Introduction

MR. LOBELL: Good morning, members of the Antiviral Committee, FDA and members of the audience.

[Slide.]

I am Ross Lobell and I work in the Regulatory Affairs Group at MedImmune. We are here today to present to you the data supporting our licensed applicant for motavizumab. To get things started, I will provide a short

introduction before moving on to the main presentation.

[Slide.]

Based on the data from our Clinical Development Program, we are proposing the following indication; motavizumab is indicated for the prevention of serious lower respiratory-tract disease caused by regulatory syncytial virus in children at high risk of RSV disease. These populations are infants with a history of premature birth, children with chronic lung disease of prematurity, and children with hemodynamically significant congenital heart disease.

[Slide.]

Synagis, a monoclonal antibody which binds to the highly conserved F protein on RSV is the only approved product for the prophylaxis of RSV. It was approved by FDA in June 1998. This product is made and marketed by MedImmune. Because RSV disease is so serious in young at-risk infants, we felt that it was important to continue to develop molecules which could provide even further improvements in reducing the occurrence of serious RSV disease and its acute sequelae.

Once palivizumab was approved, MedImmune continued

to investigate the possibility of creating a more active monoclonal antibody and eventually developed motavizumab which is similar to palivizumab but met our expectations for improved in vitro activity and binding affinity.

Motavizumab was selected to be developed as a potentially more effective agent for the prophylaxis of RSV in pre-term children.

[Slide.]

The preclinical activity of motavizumab was evaluated in a number of both in vitro and in vivo models. The body of evidence from these preclinical data all suggested an increased activity of motavizumab over palivizumab.

For example, motavizumab has about 70 times higher binding affinity for the RSV F protein and a ten-fold greater in vitro RSV neutralization activity against clinical isolates compared to palivizumab. In addition, it was shown to be more active than palivizumab in reducing RSV titers in the respiratory tract of infected cotton rats. And, in a mouse model, motavizumab also reduced RSV-induced long-term airway hyper-responsiveness.

These preclinical data led us to believe that

motavizumab has significant potential to advance our ability to prevent serious RSV disease in premature infants and also to potentially reduce some of the adverse outcomes of the disease.

In this presentation, we provide the evidence of the safety and efficacy of motavizumab relative to palivizumab which suggests we were successful.

[Slide.]

As development progressed, MedImmune engaged FDA in a number of key interactions which are shown here. Our end-of-phase-2 consultation occurred in May of 2005 and, at completion of the clinical program, a pre-BLA meeting was held and the BLA was subsequently submitted in January of 2008.

During the review process, FDA raised a number of questions which ultimately led to the issuance of a complete response letter on November 25, 2008. Developing a comprehensive response required MedImmune to visit each investigational site as well as generate additional nonclinical data to better understand the impact of motavizumab and palivizumab on the variety of available local RSV tests.

Our complete response to the CRL was subsequently submitted to FDA in December of 2009.

[Slide.]

Questions raised by FDA in the CRL primarily related to efficacy and safety. For efficacy, FDA requested additional information regarding the sensitivity and specificity of the central real-time RT-PCR assay for RSV. This was an important request since this assay was used to determine the primary endpoint of the registrational trials.

In additional, since some study physicians used local RSV testing as part of their medical care, FDA requested information regarding the possible impact of either palivizumab or motavizumab on the outcomes of locally conducted RSV tests as well as their potential to impact hospitalization decisions.

FDA also requested additional details regarding consistency of certain subgroup results within the main registration trial, MI-CP110. With regards to safety, FDA asked for external expert evaluation of the difference in the number of deaths observed between motavizumab and palivizumab as well as the reported neurologic events seen during our studies.

Additional information regarding the potential impact of motavizumab upon the assay used for ADA analysis was also requested.

Finally, the clinical study report for MI-CP124 was submitted. Based on these addition data, MedImmune requested that the indication also include the CHD patient population which was evaluated in this study.

[Slide.]

Our presentation agenda is as follows. Following my introduction, Dr. Octavio Ramilo will present an overview of RSV disease followed by presentations on efficacy, safety, benefit and risk, and we will wrap up with a discussion on our current thinking about post-approval activities.

[Slide.]

This slide lists the invited subject-matter experts who are present to help answer any questions that you may have.

[Slide.]

In addition, the following MedImmune people are also present to answer your questions. Both of these slides are in your printed deck for reference.

I will now turn the podium over to Dr. Ramilo who will present an overview of RSV disease. Dr. Ramilo is a professor of pediatrics and Chief of Pediatric Infectious Diseases at Nationwide Children's Hospital in Columbus, Ohio. In addition, he has been a bench-level and clinical researcher in the area of RSV disease for the last ten years.

Dr. Ramilo.

RSV Overview

DR. RAMILO: Thank you. Good morning.

[Slide.]

In terms of financial disclosure, as I was advised, I have been a consultant and a member of MedImmune advisory committees for about ten years. I have received grant support from MedImmune and I have participated in some of the MedImmune clinical studies.

[Slide.]

RSV is the major biorespiratory pathogen of childhood. A number of studies conducted in this country mainly have shown consistently that at least half of children get infected with RSV between their first year of life and, by the time they reach two years, about 90 percent

have at least one infection caused by RSV. And I say one because RSV infections are very common since it does not induce protective immunity.

The impact of RSV in the first year of life is significant. 25 percent of infected children develop lower respiratory-tract infections. Just to give you a flavor of the impact of RSV on health care, if we compare RSV with influenza, there is recent data indicating that RSV is associated with increased rates of emergency-room visits, hospitalizations and the impact on the care-givers of these children.

RSV causes twice as many emergency-room visits as influenza, six times more hospitalizations and care-givers of these children lost three times more work days.

[Slide.]

If we focus now on the tip of the iceberg, the most significant impact of RSV, which is hospitalizations. RSV currently, in the U.S., is the single most frequent cause of hospitalization among children. This is quite remarkable because it is more frequent than gastroenteritis, dehydration, fever or any other cause.

Data from the CDC, which are probably not very

accurate anymore, suggest that at least we have 125,000 hospitalizations every year in the U.S. I am saying that probably this data do not reflect the current situation because, in recent years, we have a number of publications from different centers around the country that suggest that the number of hospitalizations due to both bronchiolitis and bronchiolitis due to RSV are increasing.

Now, if we compare the hospitalizations, it is very important to compare the general-term children with the high-risk children. Among these, we include the three classic high-risk populations; children born prematurely, children with chronic lung disease of prematurity and children with congenital heart disease.

The rates of hospitalization in the general population are between 1 percent and 3 percent which is significantly larger in the high-risk population, between 5 percent to 10 percent. But not only these children get admitted to the hospital more frequently but also have more severe disease as demonstrated by more prolonged hospitalizations, much more frequent admissions to the ICU.

Once they get into the ICU, they stay longer and more often they require intubation and medical ventilation.

[Slide.]

One of the acute consequences of RSV is lower respiratory-tract infections. As I mentioned, the hospitalization is the tip of the iceberg but the majority of the kids that suffer bronchiolitis do not get hospitalized. That doesn't mean that they do not experience significant consequences.

RSV really has tremendous impact in the pulmonary function. We know that when you have RSV lower respiratory-tract infection, you have a smaller airway, inflammation, increased airway resistance, air trapping, atelectasis and the ventilation perfusion ratio gets altered.

This is especially significant when these RSV medically attended LRI occur in premature infants. That is why we see a tremendous increase in hospitalizations. They can develop wheezing or asthma-like symptoms throughout childhood and there is evidence very objectively demonstrated now with the new methods to assess pulmonary function in infants that there is a dramatic decrease in pulmonary function for at least one year after that acute event.

The third group that we focused on is children

with congenital heart disease. When these children get infected with RSV, they develop significant acute and persistent cardiovascular effects such as pulmonary hypertension. This really has a huge impact because it complicates their management and sometimes the corrective or palliative surgery has to be delayed.

[Slide.]

What is the current status of RSV management? Unfortunately, it is less than a year. As you well know, we do not have an effective vaccine for RSV and the management of these kids when they have an acute infection and come to the emergency room, to the clinic or the hospital, is purely symptomatic. We do not have an effective consistently used antiviral agent.

Although ribovirin is licensed for this use, we limit the use to immunocompromised patients. We do use it in our center but I can say that some other colleagues are kind of skeptical and not even using it in those situations.

So how do we decide who needs to be admitted? Just to give you a flavor, last year in my hospital alone, we had 500 hospitalizations due to RSV bronchiolitis. So it is not uncommon to have five or ten children waiting for a

bed in the emergency room. So the decision to admit is based on clinical severity.

So we try to decide who needs to be admitted based on clinical symptoms. So I don't think the determination of the RSV diagnosis has a dramatic impact as compared to the severity of the symptoms because sometimes we need more beds that we want to have. So we believe that that is the major determining factor for hospitalization.

[Slide.]

What about the standard of care for high-risk children. Palivizumab has become the standard of care for prevention of severe RSV infection across the world. It is usually given during the RSV season, one dose every month, and it was approved because of the data derived from two major double-blind, placebo-controlled trials, the IMpact Trial conducted in children with prematurity, with chronic lung disease of prematurity, and the Cardiac Trial in children with hemodynamically significant congenital heart disease.

In those two placebo-controlled trials, palivizumab showed that it can reduce hospitalizations by 55 to 45 percent. However, to this day, we do not have any

data, any drug, that can prevent the outpatient medically attended LRI. So we believe that we can achieve a further reduction in hospitalizations or decrease in the outpatient medically attended LRIs specifically in this high-risk population that would provide a significant and clinically meaningful benefit.

Now, I am going to turn the podium to Dr. Pam Griffin who is going to review the clinical efficacy data.

Efficacy

[Slide.]

DR. GRIFFIN: Good morning everyone.

[Slide.]

I am going to present the efficacy data from our registrational and supportive studies in MI-CP110 conducted in premature infants, MI-CP124 in children with congenital heart disease and MI-CP117 in healthy Native American infants.

[Slide.]

CP110 and 124 are the registrational studies for the indications in premature infants, children with chronic lung disease of prematurity, and children with hemodynamically significant congenital heart disease.

In 124, children with either a cyanotic or an acyanotic lesion were eligible for the study if the lesion was hemodynamically significant. A hemodynamically significant lesion included children who had a cyanotic lesion that was either uncorrected or partially corrected and, for children with an acyanotic lesion, there was a requirement for the presence of pulmonary hypertension or the need for medication to manage the heart disease.

117 was conducted in a different population of healthy Native American term infants who were known to be at high risk for RSV disease. This study provides important supportive efficacy and safety data.

We designed 117 to confirm the reduction in serious RSV disease with a placebo-controlled study. Now, I will mention here that a placebo-controlled study was possible in this high-risk population because palivizumab prophylaxis is not the standard of care for healthy term infants.

As you can see, these were large studies with over 9,000 children enrolled in the three studies. All three studies had a primary objective of safety. 110 and 117 also had the primary objective of the incidence of RSV

hospitalization.

To note here, 124 differs in that it was designed primarily as a safety study. It was not powered as a stand-alone efficacy study but rather results of 124 were to be taken together with results from 110 to confirm efficacy in this population of children with congenital heart disease.

Also to note here, in addition to the acute endpoints in 117, we added a secondary objective with a long-term three-year follow up to evaluate the effect of motavizumab prophylaxis on early childhood wheezing. This follow up is currently ongoing and no data are available on this endpoint.

I will present the results for each of these studies on subsequent slides.

[Slide.]

Before I present the results, I will give a brief overview of the secondary objectives in study design for the registrational and supportive studies.

[Slide.]

Here we show the secondary objectives for 110, 124 and 117. Each study is indicated at the top of the table and the objectives have been sorted by RSV-specific or non-

RSV-specific secondary objective. These secondary objectives were not prespecified as to order for the statistical analysis.

110 and 117 had the RSV-specific secondary objective of reduction of RSV outpatient medically attended lower respiratory-tract infection which I will refer to going forward as MA-LRI. 124 had two RSV-specific secondary objectives and those were reduction in the incidence of RSV hospitalization and reduction in the incidence of RSV outpatient MA-LRI.

In 110, data on the endpoint of RSV outpatient MA-LRI were collected in a prespecified subset of 2,410 patients at 133 sites. These sites were selected to be part of the subset based on their ability and willingness to collect nasal samples on all subgroups who had a medically attended lower respiratory illness.

In 124, that endpoint was added to the second season of the study. For 117, data on the endpoint of RSV outpatient MA-LRI were collected at all sites for all seasons.

As for the non-RSV-specific secondary efficacy objectives, in 110, those were the incidence of all-cause

MA-LRI, the incidence and frequency of otitis media and prescribed antibiotics for all-cause MA-LRI and for otitis media.

In 124, there were no non-RSV-specific secondary efficacy endpoints. And 117 had the non-RSV-specific secondary efficacy objectives of incidence and frequency of otitis media.

[Slide.]

Now to highlight some important aspects of the study design for the registrational studies. Both 110 and 124 were multi-national studies. 110 was conducted in the Northern and Southern Hemispheres and 124 was in the Northern Hemisphere. Both studies had palivizumab as the active comparator. Randomization was 1 to 1 and the dosing regimen was 15 mg/kg monthly for five doses for both palivizumab and motavizumab treatment groups.

Identification of RSV endpoints was accomplished as follows. Data on all hospitalizations for a respiratory illness and deteriorations due to a respiratory illness during the hospitalization were collected. Data on all outpatient respiratory illnesses with signs of lower respiratory involvement that were seen by a health-care

provider were collected.

The specific signs of lower respiratory illness were provided on the case-report form and the investigator noted the presence of these signs. These outpatient visits were unprompted and were a result of the care-taker seeking medical attention.

For both endpoints, the investigators were directed to obtain respiratory secretions within two days of the event for RSV testing by the central lab. For the most part, nasal specimens were obtained but, in an intubated patient, tracheal secretions were allowed. All RSV endpoints for the studies were determined by real-time RT-PCR which was performed by one central lab and that was Cogenics.

Real-time RT-PCR, which I will refer to going forward as PCR, was the only diagnostic assay used to identify RSV endpoints that were counted for these studies. 117, the study in Native American infants, had a similar study design and was described in detail in the briefing document. In the interest of time, I will briefly summarize here.

Identification of RSV endpoints and determination

by central PCR was the same for 117 as in the registrational studies. The dose regimen was the same at 15 mg/kg monthly for five doses. As for the differences, 117 was a placebo-controlled study with a 2-to-1 motavizumab to placebo randomization.

The children in all three studies were followed for safety and efficacy for 150 days after randomization. All three studies collected data on anti-drug antibodies and pharmacokinetics.

[Slide.]

This diagram shows the process by which respiratory endpoints were collected in 110. The process was similar for 124 and 117.

Shown here are the number of respiratory events rather than patients that were in each of the categories. At the top of the diagram are all of the protocol-specified respiratory events that were identified by site investigators and there were over 8400 such events.

These respiratory events were either respiratory hospitalizations, outpatient medically attended lower-respiratory illnesses, or outpatient medically attended upper-respiratory illnesses. Of the 724 respiratory

hospitalizations, the majority were admissions to the hospital with the remaining 18 being respiratory deteriorations which occurred during a hospitalization.

These events had samples collected for central PCR testing for RSV. Of the 2,120 outpatient medically attended lower-respiratory illness, 720 of the events were from subset sites and had samples collected for central PCR testing. Again, the subset sites were prespecified and were selected on their ability and willingness to collect samples on all patients with a medically attended lower-respiratory illness.

The remaining 1400 events were from non-subset sites and did not have PCR testing performed for the determination of study endpoints.

Data were also collected on outpatient medically attended lower-respiratory illnesses but these events did not have samples collected for central PCR testing and this was not a study endpoint.

[Slide.]

Baseline characteristics of the children in the three studies were balanced between treatment groups. Patients were randomized by site and stratified by the

presence or absence of chronic lung disease of prematurity in 110 and the presence or absence of a cyanotic heart lesion in 124.

In 110, about 20 percent of the children enrolled in both treatment groups had chronic lung disease of prematurity. In 124, just over 50 percent of the children in both treatment groups were enrolled in the cyanotic stratum.

Study compliance was high and similar between the treatment groups for all three studies for children who completed the study and for those who received all five scheduled doses of study drug.

In 110, approximately 98 percent of patients completed the study and about 97 percent received all five doses of study drug.

[Slide.]

Now we will move into the efficacy results for RSV hospitalization and RSV outpatient MA-LRI.

[Slide.]

Before I present the efficacy results, I will briefly describe the considerations for the statistical analysis for the primary endpoint of RSV hospitalization in

110 and 124. I will begin with 110 shown on this slide.

110 had the active comparator, palivizumab, which is known to be efficacious in preventing RSV illness, and palivizumab is the standard of care in premature infants. Data from the two prior placebo-controlled palivizumab studies in premature infants and in children with congenital heart disease were used to determine a noninferiority margin.

As requested by the FDA, the noninferiority margin was determined using the 95-95 confidence interval statistical method to preserve at least 50 percent of the benefit observed for palivizumab over placebo in the previous palivizumab studies.

Noninferiority of motavizumab compared with palivizumab required the upper bound of the 95 percent confidence interval for the relative risk of RSV hospitalization to be less than 1.265.

The statistical analysis for noninferiority was performed first and, if that was met, then superiority was tested. On the schematic shown here, the X axis is the relative risk of RSV hospitalization with motavizumab versus palivizumab. Values to the left favor motavizumab and, if

the upper bound of the 95 percent confidence interval was less than 1.265, then noninferiority would be demonstrated.

If the upper bound of the 95 percent confidence interval was less than 1.00, then superiority would be demonstrated.

[Slide.]

Now for 124. As mentioned previously, 124 was not powered as a stand-alone efficacy study but rather results were to be pooled with 110 to determine the efficacy in children with congenital heart disease. Pooling of the efficacy data was appropriate as the studies had similar designs, study endpoints and sample collection for testing for RSV.

Prior to pooling the data, interaction tests demonstrated no evidence of a difference in treatment effect across the study populations of premature infants with chronic lung disease, premature infants without chronic lung disease and children with congenital heart disease.

This analysis was prespecified prior to unblinding. The same noninferiority margin of 1.265 was used because that margin had been determined using data from both premature infants and children with congenital heart

disease studied in the previous placebo-controlled palivizumab studies.

[Slide.]

The results for RSV hospitalization are shown here for 110 in premature infants, 124, children with congenital heart disease, and 117, the Native American infants. To point out here, 117 is separated since it was a placebo-controlled study and 124 and 110 had the active comparator, palivizumab.

To orient you to the slide, these bar graphs represent the incidence of RSV hospitalization. Within the bars are the numbers of patients who had an RSV hospitalization. Palivizumab, active comparator in 110 and 114, is shown in green. Placebo is represented as gray and motavizumab is in orange. The color scheme for treatment groups is the same on all subsequent slides.

The table below the bar provides the relative risk, 95 percent confidence intervals and efficacy demonstrated by motavizumab for each of the studies.

I will begin with 110, the study in premature infants.

As shown here, the incidence of RSV

hospitalization in palivizumab recipients was 1.9 percent compared with 1.4 percent in motavizumab recipients. In premature infants, the relative risk of an RSV hospitalization with motavizumab compared with palivizumab was 0.74. The upper bound of the 95 percent confidence interval was 1.08 which met our noninferiority criteria with a p-value for noninferiority less than 0.01.

124, the study in children with congenital heart disease, is shown next and, again, was not powered as a stand-alone study to show statistical significance for efficacy. The rate of RSV hospitalization in palivizumab recipients was 2.6 percent compared with 1.9 percent in motavizumab recipients.

This relative reduction of 25 percent is similar to and consistent with the 26 percent relative reduction seen in 110 and provides support for the results in premature infants.

117 is the only placebo-controlled study and of note here is that the rate of RSV hospitalizations in placebo recipients was 8.3 percent. As you heard in Dr. Ramilo's presentation, this RSV hospitalization rate is similar to the placebo rate seen in the historical

palivizumab studies.

In this study, there was an 83 percent relative reduction in the incidence of RSV hospitalization in children who received motavizumab compared to those who received placebo. This was significant at p less than 0.0001 demonstrating motavizumab's superiority over placebo.

[Slide.]

In addition to the incidence of RSV hospitalization, we were also interested in the severity of illness during the RSV hospitalization. Here we present results of a post hoc analysis for severity of illness in the children in 110 who were hospitalized with an RSV illness. These are all of the children in 110 who had an RSV hospitalization. There were 62 in the palivizumab group and 46 in the motavizumab group.

We looked at a number of parameters that would indicate the severity of the illness during RSV hospitalization. As on the previous slide, palivizumab is in green and motavizumab is in orange.

The bar graph on the left shows the percentage of patients who had an RSV hospitalization and who also required additional support, supplemental oxygen, shown

here, admission to the intensive-care unit or mechanical ventilation.

The bar graph on the right displays the mean duration in days of the RSV hospitalization, time on supplemental oxygen, stay in the intensive-care unit and duration of mechanical ventilation.

These results indicate that the severity of illness in motavizumab recipients who had an RSV hospitalization was no worse than for palivizumab recipients. And there is a suggestion that the illness in the motavizumab recipients may have been attenuated.

Again, while this was a post hoc analysis and the number of hospitalized children is small, the results appear to favor motavizumab.

[Slide.]

Before I present the results for the endpoint of RSV outpatient MA-LRI, I would like to present the baseline characteristics for the children in 110 who participated in the subset data collection for that endpoint and for those who were in the non-subset population.

This table is set up with the subset and non-subset populations indicated here with the treatment groups

just below. As shown here, baseline characteristics were balanced for the children who were part of the subset and for those who were in the non-subset population. Baseline characteristics were also balanced between treatment groups for each population.

Again, about 20 percent of the children in both treatment groups and in both populations had chronic lung disease of prematurity.

So the children who participated as part of the subset for the endpoint of RSV outpatient MA-LRI were very representative of the entire population. Also to note here, no site had a mix of patients participating and not participating in RSV outpatient MA-LRI data collection during the same season.

[Slide.]

Now for the efficacy results for RSV outpatient MA-LRI. This slide is set up like the previous efficacy slide on RSV hospitalization. Here the bars represent the incidence of RSV outpatient MA-LRI, 110, 124 and 117. Again, 117, the placebo-controlled study, is separated from the two studies that had the active comparator, palivizumab.

Again, the table below the bars provides the

relative risk, 95 percent confidence intervals and the efficacy demonstrated for motavizumab for each of the studies.

In 110, the incidence of RSV outpatient MA-LRI in palivizumab recipients was 3.9 percent compared with 2 percent in motavizumab recipients. This was a 50 percent relative reduction in the incidence of RSV outpatient MA-LRI in motavizumab recipients. The relative risk was 0.5 and the upper bound of the 95 percent confidence interval was less than 1.00 with an unadjusted p-value of 0.005.

Since this is an RSV-specific endpoint, this result provides supportive evidence for the anti-RSV activity and efficacy of motavizumab.

Next, for 124, as you can see the number of patients with congenital heart disease who had this endpoint is small. However, the results for this endpoint are similar to and consistent with the results seen in 110 providing support for the results in premature infants.

In 117, of note here is that the rate of RSV outpatient MA-LRI in placebo recipients was 9.5 percent. There was a 71 percent relative reduction in the RSV outpatient MA-LRI in children who received motavizumab

compared to placebo.

Again, this was significant at p less than 0.001 demonstrating motavizumab's superiority over placebo. These results from a placebo-controlled study provide support for the effectiveness of motavizumab in reducing serious RSV disease.

[Slide.]

We performed subgroup analyses for the incidence of RSV hospitalization. Shown here are the results of that analysis in premature infants in 100. This forest plot displays the point estimates and 95 percent confidence interval for the relative risk of RSV hospitalization with motavizumab compared with palivizumab for each of the subgroups. The relative risk of an RSV hospitalization is shown on the X axis. The vertical white line indicates a relative risk of 1.00.

The subgroups shown are the presence or absence of chronic lung disease of prematurity, gestational age with the division at 32 weeks, and regions which have been divided into the Northern Hemisphere and Southern Hemisphere with the U.S. and European Union shown as subsets of Northern Hemisphere.

The first line of the plot represents our primary efficacy analysis for RSV hospitalization, the point estimate of 0.74. These subset point estimates for the relative risk of RSV hospitalization in motavizumab recipients compared to palivizumab recipients are consistent with noninferiority with the majority occurring at or below 1.00

As for the geographic regions, as shown here for each of the regions, the point estimates for RSV hospitalization are less than 1.00 with the exception of the U.S. where the point estimate is slightly above 1.00. However, as I will show on the following slide, for the U.S., the point estimate for RSV outpatient MA-LRI is well below 1.00.

In addition, the point estimates for the European Union and the Southern Hemisphere are less than the primary efficacy analysis point estimate of 0.74. While not shown here, the regions studied on the Southern Hemisphere were South America and Australia and New Zealand. The point estimates for RSV hospitalization are less then 1.00 in all of those regions.

[Slide.]

Similar to RSV hospitalization, we performed subgroup analyses for the incidence of RSV outpatient MA-LRI and, again, the results for 110 are shown here. These results are shown as a forest plot with point estimates and 95 percent confidence intervals and we examined the same subgroups as in RSV hospitalization. For baseline characteristics subgroups, as you can see, all of the point estimates for this endpoint are less than 1.00.

For the subgroup of premature children without chronic lung disease and for the gestational age subgroup less than or equal to 32 weeks, the upper bound of the 95 percent confidence interval is also less than 1.00.

As for regions, as I mentioned on the previous slide, the point estimate for the U.S. subgroup for RSV outpatient MA-LRI is well below 1.00. In fact, for the RSV outpatient MA-LRI endpoint by regions, we find that all of the point estimates favor motavizumab.

We know of no biologically or medically plausible reason for motavizumab to have a different treatment effect by region. Moreover, the region-specific data are consistent with the overall study conclusion that the efficacy of motavizumab was noninferiority to palivizumab in

reducing the incidence of RSV hospitalization.

The results for RSV outpatient MA-LRI provide support for the anti-RSV activity and efficacy of motavizumab.

[Slide.]

Results for the non-RVS-specific secondary endpoints in 110 and 117 are shown in this table. As you recall, in 124, there were no non-RSV secondary efficacy endpoints.

Results for the incidence of all-cause MA-LRI and the incidence and frequency of otitis media are presented as the percentage of patients who had that endpoint. Prescribed antibiotics for all-cause outpatient MA-LRI and prescribed antibiotics for otitis media are presented as the mean and standard error.

None of these all-cause secondary endpoints were significantly different between treatment groups.

[Slide.]

Next we present the considerations for the identification of RSV hospitalization endpoints. Specifically the question here is regarding the potential effect of RSV testing which may have been performed locally

on the sites on hospital admissions. This topic was discussed in detail in the briefing document and I will provide a brief summary here.

[Slide.]

We evaluated all respiratory illnesses that had local RSV testing performed. This would be important in the context of admitting physicians using a local test result as the basis for the decision to hospitalization a patient.

During the motavizumab clinical studies, physicians obtained local RSV testing as they desired. It was not protocol-directed and the data on local testing were obtained after the study completion to answer the question from the agency regarding the potential influence of local tests on hospital admission.

For this analysis, a false-negative result is defined as a negative local RSV test with a positive PCR result. As background on this topic of false-negative local tests, of note is that it was determined that both motavizumab and palivizumab could decrease detection of RSV in the commonly used RSV test BinaxNOW.

Because of this, before the start of the study, investigators were notified that a negative result from a

Binax test might be a false-negative.

As you recall, earlier I showed the flow diagram for the process of collection of respiratory events in 110. We collected the same information for 124 and 117. As for the information on local RSV testing, we collected and analyzed more than 12,000 respiratory events in the three studies with data available for 95 percent or greater of the medically attended outpatient respiratory events in the three studies.

[Slide.]

Since 110 was the largest study of the three, that is where we have the largest amount of information on local RSV testing. In the interest of time, I will present the findings from 110. The results were similar for 124 and 117.

In 110, local RSV testing was performed for approximately 11 percent of the respiratory events in both palivizumab and motavizumab recipients. Of the local tests that were performed, over 80 percent were negative for both treatment groups.

Of note, children were hospitalization at a similar frequency with either negative or positive local

test results. As seen here, of the respiratory events with local testing performed, approximately 50 percent of the events were associated with a hospital admission regardless of whether the test result was negative or positive. That was for both groups.

When we analyzed our clinical-study data on local RSV test and PCR using PCR as the gold standard, we found that there were, indeed, more false-negative local RSV tests in the motavizumab group than in the palivizumab group.

For RSV hospitalizations, the percentage of palivizumab recipients with false-negative local RSV results who were admitted was approximately 15 percent compared to about 41 percent in the motavizumab recipients. This indicates that motavizumab recipients with false-negative local RSV results were being admitted to the hospital.

Next we looked at the clinical reasons for hospital admissions in those patients who had local testing for RSV to confirm that these children were truly ill. For 95 percent or more of patients, there was a clear clinical reason for the admission with the majority of patients admitted due to the need for acute respiratory care such as oxygen, mechanical ventilation and ICU care.

These analyses suggest that, while motavizumab may cause false-negative results with local RSV test, this did not affect the decision by the clinician on whether or not to hospitalize a child with a respiratory illness. As you heard also from Dr. Ramilo, respiratory illnesses can be caused by pathogens other than RSV and clinicians are likely to make a decision to hospitalize or not based on the clinical signs of illness.

[Slide.]

As a final analysis, sensitivity analyses were performed to evaluate the potential effect of a false-negative local RSV test on hospital admission. In the interest of time, I will present the summary of the analysis for 110. If you would like more detail on the methods and results for these sensitivity analyses, then we would be glad to provide that during the question-and-answer session.

Sensitivity analyses were performed for all outpatient medically attended lower-respiratory illnesses. These analyses, based on all outpatient medically attended lower-respiratory illnesses, represent the conservative assumption that all of these illnesses with false-negative local RSV test results could have been hospital admissions

if the event had been reported with the positive local test.

Additionally, sensitivity analyses were performed to include all medically attended lower-respiratory illnesses and combined medically attended lower-respiratory illnesses with medically attended upper-respiratory illnesses. When the analyses are expanded to include all outpatient upper-respiratory illnesses, the assumption that all of these upper-respiratory illnesses with false-negative local RSV test results could have been hospital admissions is even more conservative because upper-respiratory illnesses are not likely to result in hospitalization.

Four imputation methods were used for the analyses and those were all known false-negatives and the imputation of a proportion of unknowns using a point estimate 95 percent confidence interval and 100 percent of missing events.

Now for the results of these analyses. For the sensitivity analyses that were performed using all medically attended upper- and lower-respiratory illnesses, all of the upper bounds of the 95 percent confidence intervals are less than the noninferiority margin of 1.265 with the exception of one analysis based on the point-estimate method for

imputation of a proportion of events where it was unknown if the local RSV test was a false-negative.

Here the upper bound of the 95 percent confidence interval is 1.46. Since there is a higher rate of false-negative local RSV test in motavizumab recipients, this result was driven by the imputation of a higher proportion of motavizumab patients with unknown local RSV test results under the assumption that they were false-negatives.

For the sensitivity analyses that were performed using all medically attended lower-respiratory illnesses and did not include the upper-respiratory illnesses, all of the upper bounds of the 95 percent confidence intervals are less than the noninferiority margin of 1.265.

In conclusion, both sets of sensitivity analyses using either medically attended upper- and lower-respiratory illnesses or lower-respiratory illnesses alone demonstrated that, for all imputations, with one exception that included an extreme assumption, the results remain consistent with the primary efficacy analysis for noninferiority of motavizumab compared with palivizumab in preventing RSV hospitalization.

[Slide.]

Next we present a summary of the RSV efficacy endpoints for the registrational and supportive studies.

[Slide.]

The RSV-specific endpoints for the three studies are shown on this forest plot with the registrational studies 110 and 124 grouped together and the supportive placebo-controlled study 117 shown separately.

These individual study results were shown on previous slides but not in this format. The new information shown here is 110 and 124 pooled for RSV hospitalization and 110 and 124 pooled for RSV outpatient MA-LRI. The vertical yellow line indicates the noninferiority margin of 1.265 and applies only to RSV hospitalization for 110, and 110 and 124 pooled. Values to the left favor motavizumab.

Of particular note is that all of the point estimates of the relative risk for both endpoints in all of the studies are less than 1.00.

In addition, for the studies that were powered for efficacy, all the 95 percent confidence interval upper limits are less than 1.00 with the exception of RSV hospitalization in 110, as noted previously, and in 110 and 124 combined. The upper limits for these confidence

intervals are well below the noninferiority margin of 1.265.

As for 110 and 124 combined, for RSV hospitalization and for RSV outpatient MA-LRI, as expected, the results of the combined studies are very similar to the results seen in 110 alone, combined 110 alone for RSV hospitalization, combined 110 alone for RSV outpatient MA-LRI.

So, as you can see, motavizumab recipients had consistently lower rates of RSV hospitalization and RSV outpatient MA-LRI in all of the studies individually and 124 combined.

[Slide.]

In conclusion, based on efficacy data from the registrational studies in premature infants and in children with congenital heart disease and the supportive study in Native American infants, motavizumab has been shown to be effective in decreasing serious RSV lower-respiratory disease in high-risk children.

In premature infants, motavizumab was noninferior to palivizumab in reducing the incidence of RSV hospitalizations and there was supportive evidence for efficacy in the reduction of RSV outpatient MA-LRI. Studies

in children with congenital heart disease and Native American infants provide additional supportive data for the efficacy of motavizumab.

Now, Dr. Gennie Losonsky will present the safety data from our motavizumab studies.

Safety

[Slide.]

DR. LOSONSKY: Good morning.

[Slide.]

During this presentation, I will review the safety findings from the principal motavizumab studies covering drug exposure, giving you an overview of AEs, deaths, skin reactions and skin adverse events associated with anti-drug antibody.

[Slide.]

The pediatric safety database for motavizumab exposures includes over 5,000 subjects, the majority coming from the three principal safety and efficacy studies, CP110, 124 and 117.

[Slide.]

This slide present the overall adverse-event profile of motavizumab and controls in these studies and is

a summary of the more detailed adverse-event data reported in our briefing book.

The three main studies are arranged in columns by treatment at the top with the type of AEs represented in columns on your left. This representation is used consistently throughout this presentation. Subject numbers and rates of patients with one or more AEs are presented in the body of table.

As you can see from the top row, 85 percent of patients across the three studies had at least one adverse event with similar rates in each treatment group within each study. Level 3 events are those requiring immediate medical attention. Level 4 events are considered life-threatening events with medical intervention required to support vital functions.

The frequency of level 3 and 4 AEs and SAEs were also similar within treatment groups for each of these three studies with no appreciable rate differences noted between groups.

There were high rates of level 3 and 4 events in the Cardiac study due to complications from this population's underlying heart disease. The types of AEs and

SAEs were illnesses expected for these populations.

Deaths due to all-causes were infrequent with similar rates between treatment groups within each study. Deaths occurred in a total of four pre-term patients in the palivizumab group and eight patients in the motavizumab group in CP110 with frequencies of 0.1 and 0.2 percent respectively.

Similar rates of deaths were seen in motavizumab and control treatment groups in CP124 and 117. Overall, these mortality rates and types of deaths were expected for these populations. There were no RSV-related deaths. The frequencies of sudden unexplained deaths, or SIDS deaths, in premature infants in CP110 were also low and within expected frequencies reported in four motavizumab recipients and two palivizumab recipients.

In the Cardiac study, there were no SIDS events and the sudden-death rates were low and evenly distributed by treatment. There were no sudden deaths reported in the Native American study.

A more detailed discussion of these events including the blinded and unblinded external medical experts' review are in Section 4.7 of your briefing book.

This review concluded that the mortality rates and types of events leading to deaths were consistent with these study populations.

[Slide.]

This table shows the individual adverse events resulting in dosing discontinuation. The overall rate of dosing discontinuation is presented in the top row and was low and similar between treatment groups in CP110 with few events in CP124 or 117. We note that, in CP110, nine of the 13 patients treated with motavizumab had dosing discontinuation for events consistent with possible hypersensitivity.

One patient treated with palivizumab in CP124 and one patient treated with motavizumab in 117 also had dosing stopped for such events. These adverse events were confined to the skin or soft tissues. All recurred within two days of dosing. None were life-threatening and all resolved without sequelae.

[Slide.]

AEs in the skin and subcutaneous tissue system organ class were significantly increased by about two percentage points in motavizumab recipients compared to

palivizumab in CP110.

[Slide.]

Similar, but not significantly different, treatment-group rate differences were seen in CP124 and 117. Possible contributors to this difference were identified as AEs of rash and urticaria. Our analytical approach is summarized here and also in the briefing book. It made use of the standard MedDRA Queries of terms for angioedema and anaphylaxis that provided the category of specific skin-event terms consistent with possible hypersensitivity.

This category was supplemented by other possible hypersensitivity event terms from the immune disorders SOC. Nonspecific rash events were the remainder of the terms that might be consistent with nonspecific rashes or soft-tissue swelling obtained from the skin and subcutaneous tissue SOC.

Events were further characterized by their timing relative to dosing. A time period of two days was used to conservatively capture those events that might be consistent with an acute immediate hypersensitivity event. Possible respiratory hypersensitivity events were sought using a similar approach.

[Slide.]

This slide is an overview of our main analysis. The top row represents the number of children with a report of at least one skin adverse event of interest. As you can see, over 5 percent of children in each treatment group across the studies including placebo recipients had a skin adverse event of interest.

Within each study, reports of such events were increased by about 2 to 3 percentage points in motavizumab patients compared to controls. Level 3 or SAE events were seen in six to 14 motavizumab recipients across all studies for rates of 0.4 to 1.3 percent. These were at higher frequencies compared to controls.

There were no life-threatening level 4 events reported in motavizumab recipients in these studies. Dosing discontinuations due to skin events were captured as previously described.

The rates of both nonspecific rashes and specific events were also increased in patients treated with motavizumab in these three studies. Across all studies, the majority of skin events were non-specific rashes accounting for 70 percent or more of all skin adverse events of

interest.

In motavizumab recipients, regardless of when these nonspecific events occurred relative to dosing, these events did not result in dosing discontinuations. 99 percent were level 1 or 2 in severity and recurrences were infrequent, less than 10 percent.

The remainder of the skin events of interest were specific skin events which were increased in motavizumab recipients across these trials. In this category, no events consistent with a severe cutaneous reaction such as Stevens-Johnson syndrome, toxic epiderimal necrolysis or erythema multiforme major were observed.

Specific skin events occurring beyond two days were the majority of events seen in active and placebo-controlled groups and occurring at similar frequencies. Patients with events occurring beyond two days generally had alternative etiologies or were redosed by the site investigators without recurrences.

I will be discussing the specific skin events occurring within two days in more detail shortly.

[Slide.]

But first, I would like to present the timing of

skin adverse events by treatment, dose number and skin-reaction type as seen in pre-term patients in CP110.

The graph on the left presents all skin events by type occurring at any time by dose. The graph on your right presents those specific skin events consistent with possible hypersensitivity occurring within two days of dosing by dose. Palivizumab events are in green and motavizumab events are in orange. The darker bars indicate nonspecific rash events and the lighter bars indicate specific events consistent with possible hypersensitivity.

Patient numbers are displayed within or above the bars. Both graphs demonstrate that the rate of skin events, regardless of skin type, did not increase over time with increased drug exposure.

Looking at the graph on your left, following dose 1, both palivizumab and motavizumab recipients have both types of skin events with more motavizumab recipients with events of either type. Generally, this pattern is repeated throughout subsequent doses with no evidence of an increase in skin-event rate with repeat dosing.

The data presented in the graph on your right which is also for those events consistent with possible

hypersensitivity occurring within two days of dosing has similar findings. Although not shown in this slide, similar findings are seen for events of higher severity or seriousness.

In our view, these data do not support an immune-based mechanism for these events.

[Slide.]

This table presents the characteristics of skin events occurring within two days of dosing in our three main studies. Subjects with nonspecific skin-rash events are summarized on the top row. Specific skin events of possible hypersensitivity are on the bottom three rows.

About half of the skin reactions in all subjects in this time period were nonspecific rash events although one such event resulted in dosing discontinuation in a palivizumab recipient in CP124. For motavizumab recipients, these events had little severe clinical consequences. There were no dosing discontinuations. Recurrences were infrequent and of no increased severity.

Few were considered related and less than 10 percent were treated by the site physicians. As for the specific events, seen on the bottom, there was a low but

increased rate of these skin reactions in motavizumab recipients compared to active controls, 0.7 to 1.0 percent of motavizumab patients compared to 0.2 percent active controls with no events seen in placebo recipients.

Only patients given motavizumab had events considered more severe or serious. These rates were less than 1.0 percent. There were no life-threatening events, level 4, reported in these three studies for motavizumab recipients.

For patients given motavizumab, treatment was initiated in about 50 percent consisting primarily of oral antihistamines or steroids. All these events resolved by about half within three days with no sequelae.

As mentioned previously, dosing was discontinued for events occurring in this time period. Recurrences occurred in a minority of patients who were re-dosed and these recurrent events were no more severe compared to the initial event. There were no events of respiratory hypersensitivity.

[Slide.]

This slide presents all of the serious or severe skin reactions reported in motavizumab recipients occurring

on the day of dosing. It includes clinical findings, treatment given, and resolution onset from the AE onset. For the latter variable, events that only have time to complete resolution in our database are footnoted.

Clinical findings for these cases were confined to the skin or subcutaneous tissue although I will talk about two events that had respiratory components.

There was no evidence of anaphylaxis for any of these events as no event had new onset post-dose systemic signs or symptoms consistent with anaphylaxis. Epinephrine, which is the treatment choice for anaphylaxis, was not used by treating physicians for these events. In contrast, antihistamines or steroids or no treatment was initiated for these events.

Resolution onset was quite rapid for some events and apparently self-resolving for some of these events that were not treated. One patient in the Cardiac study was noted to have hoarseness. This child had normal vital signs, no respiratory distress and had a rapid onset of resolution.

One Native American patient was noted to have right upper-lobe wheezing during one of these events. This

child had known reactive airway disease prior to enrollment and was on Singulaire and bronchodilator therapy the week before dosing for a recurrent wheezing illness.

Prior to dosing on the day of dosing no wheezing was noted, however. Post-dose right upper-lobe wheeze was noted during the physical-exam evaluation for the skin reaction. Oxygen saturations were normal as were the vital signs and he was treated for an upper-respirator illness. Our assessment of the relatedness of the local wheeze to study drug is confounded by the child's recurrent wheeze respiratory history and the concurrently diagnosed upper-respiratory illness.

[Slide.]

One additional case is presented as the FDA reviewed this as an event of anaphylaxis occurring in our second season dosing study, CP118. This study enrolled pre-term infants who received motavizumab in the first season in CP104. This patient had an onset of skin rash and some eyelid swelling post dose 3. She was described as having a dry cough with no stridor.

The site reported to us that the vital signs taken at 20 minutes post this dose or five minutes after the start

of the event were normal. The pre and post dose vital signs are presented here. There was no respiratory distress noted. There were lower blood-pressure measurements post dosing but we note that the systolic blood pressure of 80 to 90 is considered normal for a child this age.

So the pre-dose systolic blood pressure of 125 is distinctly abnormal and might reflect the agitating effects of study procedures. Post dose, she had no compensatory increase in heart rate that would be expected if the blood pressure was falling and anaphylaxis was ensuing. Epinephrine was not initiated by the site investigator consistent with her assessment that the vital signs were normal.

Rather, antihistamine treatment, which is indicated to relieve skin and soft-tissue manifestations of allergy, was given 30 minutes after AE onset. The child's adverse event resolved rapidly without sequelae. Clinically, this presentation, timing of treatment, type of treatment used, are inconsistent with a life-threatening event of anaphylaxis.

When the Sampson Guidelines were applied to this event, it did not meet the criteria for anaphylaxis.

[Slide.]

The frequency of detectable ADA or anti-drug antibody in motavizumab- and palivizumab-treated patients was low, occurring in less than 10 percent of treated individuals.

[Slide.]

Only one child with anti-drug antibody to motavizumab had an IgE response detected and that was in a term Native American child in CP117 who had no significant associated adverse-event findings.

There were no associated safety findings in children with ADA to palivizumab. Although the overall AE profile was similar between motavizumab recipients with and without ADA, there were skin reactions associated with motavizumab anti-drug antibody.

As only three of the nine children with motavizumab ADA in CP124 had any skin AEs and there were no skin reactions for the three subjects in CP117 who had ADA to motavizumab, I will now present the data from CP110.

[Slide.]

In CP110, 17 of the 58 children with ADA to motavizumab had a skin adverse event of interest

representing an increased rate compared to those without ADA. Specific skin events temporally associated with dosing and those skin events of higher severity were also increased in motavizumab recipients with ADA compared to those without ADAs.

Motavizumab patients with ADA and a skin event accounted for less than 10 percent of all patients with any skin event of interest. In addition, as the rate of immunogenicity was low, the absolute number of patients with these more significant events was either the same or higher in motavizumab recipients without ADA compared to those with ADA making it impossible clinically to differentiate patients with ADA by their skin clinical presentations. Lack of recurrence with redosing was also seen in some patients with ADA.

[Slide.]

Data from over 5,000 high-risk patients receiving motavizumab demonstrates it to have a similar safety profile to palivizumab except for higher rates of skin reactions of possible hypersensitivity.

[Slide.]

Specifically, there were similar rates and types

of AEs, level 3-4 AEs and SAEs compared to palivizumab. The rate of dosing discontinuation was low, less than half a percent, and similar between active treatments although we do note that the reasons for dosing discontinuations were different in motavizumab recipients.

Overall, mortality was low and consistent with these pediatric populations. Skin events consistent with possible hypersensitivity occurring within two days of dosing were infrequent but at a higher incidence in patients receiving motavizumab. These events and those of higher severity occurred in less than 1 percent of motavizumab recipients across all studies.

These events appeared to be readily identifiable, clinically easily managed primarily with oral antihistamines, steroids or no treatment, and all resolved without sequelae.

In patients treated with palivizumab or motavizumab who were re-dosed after initial event, recurrences were infrequent leaving the mechanism of these reactions unclear.

Thank you very much for your attention.

I would now like to turn over the podium to our

two clinicians, Dr. Mark Boguniewicz, who is professor of pediatrics, Division of Pediatric Allergy/Immunology, National Jewish Health and the University of Colorado School of Medicine, and that will be followed by Dr. Ramilo who spoke about the RSV disease burden. He will discuss the potential benefits of motavizumab.

Risk Assessment

DR. BOGUNIEWICZ: Good morning.

[Slide.]

I am Mark Boguniewicz. I am professor of pediatrics in the Division of Pedestrian Allergy/Immunology at National Jewish Health and the University of Colorado School of Medicine. I have over 25 years of experience treating children with the spectrum of allergic and immunologic diseases.

By way of disclosure, I have been asked to be here today by MedImmune as a paid consultant.

[Slide.]

The data presented today show that motavizumab and palivizumab have similar overall safety profiles. One potential risk factor for motavizumab compared to palivizumab was identified and that is the increased but low

rates of skin reactions with some features suggestive of immediate-type hypersensitivity reactions observed.

However, these were predominantly of mild severity, easily managed primarily with antihistamines. And, of note, none of the patients were treated with epinephrine.

Furthermore, these were transient in nature and in approximately 90 percent of treated patients, they did not recur. If they did recur, they were no more severe than the initial events.

So, in my opinion, as a clinician allergist/immunologist, the reported adverse events were, in fact, not severe and were easily managed with routine pediatric medications.

Benefit Assessment

[Slide.]

DR. RAMILO: In summary, as a clinician who takes care of children with RSV infection, I believe that the totality of the data presented demonstrates that motavizumab is effective in decreasing serious RSV infection in high-risk children.

The reduction of RSV hospitalization demonstrates

that motavizumab is superior to placebo and noninferior to palivizumab. In addition, the reduction of RSV outpatient MA-LRI demonstrates that motavizumab is superior to placebo and palivizumab and offers an additional benefit suggesting that motavizumab may provide a long-term benefit in this population.

In summary, I believe the data indicates that the clinical benefit that motavizumab provides to this high-risk population outweighs the management of risk.

Thank you very much.

Post-Approval Activities

DR. GEBA: Good morning.

[Slide.]

I lead the Clinical Development Group at MedImmune. My name is Greg Geba. I am sure you can see the enthusiasm we have for motavizumab which represents a further advance in the prophylaxis of serious RSV disease in children at risk.

My goal is to describe the post-approval activities that MedImmune will make in supporting motavizumab which aim to promote proper use, detect serious adverse events and implement any necessary safety measures

expeditiously.

[Slide.]

You have been presented data on the efficacy of motavizumab in decreasing the incidence of serious RSV disease. As you heard during the description of the safety profile of motavizumab compared to palivizumab, there was a greater proportion of patients reporting events related to the skin, some of which were severe and some few, which led to withdrawal

To help health-care providers manage these infrequent events, MedImmune recommends that prescribing physicians permanently discontinue therapy for skin reactions temporally associated with motavizumab administration which are serious, require immediate medical attention or are life-threatening.

We would advise physician discretion in assessing whether to continue therapy for less severe events which are temporally associated and possibly related to motavizumab. For those reactions not temporally associated with motavizumab administration but possibly related, as with any drug, we would recommend that the potential benefits and risks be weighed in deciding whether or not to continue

therapy.

[Slide.]

Upon approval of motavizumab, MedImmune will take steps to ensure targeted assessment of the safety profile focusing on skin and hypersensitivity reactions. In addition, as pursued in the postmarketing surveillance for palivizumab, MedImmune will proactively monitor for other potential and unknown safety signals and events which are rare but may be clinically important or significant.

To accomplish this, MedImmune plans to manage risk using the following elements. First, we will educate prescribers and health-care providers. We will pursue enhanced routine pharmacovigilence activities--that is, those activities that are beyond the pharmacovigilence that is normally pursued. We will enhance that pharmacovigilence.

And we will conduct focused phase 4 studies to prospectively monitor for and characterize skin events and perform a retrospective cohort study to detect rare adverse-event signals.

[Slide.]

MedImmune believes it is critical to carefully

educate prescribers regarding the safe and effective use of its products. For motavizumab, MedImmune has included specific text in the package insert which describes recommendations for safety monitoring and product use or discontinuation.

MedImmune plans a medical education campaign employing physician specialists who will train health-care providers on the appropriate use of the product and all safety-related considerations as specified in the package insert.

MedImmune has over twelve years of experience in passive reporting and routine pharmakovigilence with Synagis and has found this technique effective in capturing emerging safety signals in the postmarketing environment. For motavizumab, MedImmune plans to take a similar approach but, in addition, plans to expedite all serious adverse events of special interest agreed to with FDA for the first three years that motavizumab is on the market.

To improve the quality of data collected, all reports of adverse events of special interest--that is, both serious and non-serious adverse events--will also be subject to a targeted questionnaire to assure accurate and complete

systematic capture of information.

Finally, MedImmune will follow up on serious adverse events that are related to severe hypersensitivity or serious life-threatening skin reactions to determine whether or not prescribers discontinued product as recommended in the package insert and to determine if additional safety information can be obtained from these cases.

In addition, MedImmune plans to establish an expert panel to adjudicate skin adverse events, skin serious adverse events, in order to confirm diagnosis provided by clinicians in the field and to help monitor overall skin safety observed in the postmarket period. We will reassess these pharmacovigilence plans after three years.

[Slide.]

To augment our pharmacovigilence plans, MedImmune plans to conduct at least two post-approval studies. The first is a prospective study to characterize skin and hypersensitivity events, their incidence rate and severity, and would also be used to determine the presence of motavizumab-resistant RSV.

In this study, a network of clinical centers could

be used to enroll motavizumab recipients at the time of their first dose and follow patients for 30 days after their last dose. Subjects would return to clinic upon occurrence of a skin or hypersensitivity event for thorough evaluation and characterization.

The second study is a retrospective cohort study using large claim databases to assess adverse events during motavizumab use in the real-world setting. This study will involve over 30,000 motavizumab recipients and matched controls powered for the detection of rare events--that is, those occurring on the order of 1 in 10,000--as well as to identify potential predictors of adverse events.

The information will also be used to assess whether any safety signals can be detected when motavizumab and palivizumab are dosed sequentially in the same patient or to monitor for the safety of motavizumab administered to the same child in sequential seasons.

During the course of implementing the different components of our plan, any emerging risk or benefit information will be thoroughly evaluated and revisions of the plan will be implemented immediately as necessary.

[Slide.]

In closing, MedImmune appreciates the opportunity to present to this committee today and would like to leave you with our conclusions.

Given the efficacy shown in these studies and an acceptable and manageable safety profile, motavizumab represents an effective immunoloprophylactic against serious RSV disease in high-risk children. Data relating to inpatient and outpatient serious RSV outcomes suggest that motavizumab is the agent of choice for immunoprophylaxis of serious RSV infection in children and our postmarketing and pharmacovigilance plan and post-approval studies described before will permit timely and systematic collection and assessment of safety data emerging from the marketplace.

So, on behalf of MedImmune and all the presenters today for motavizumab, we thank you very much.

DR. HENDRIX: Thank you for the sponsor presentations.

Before I open the speakers for questions of clarification from the panel, there are two members that showed up that did not get a chance to introduce themselves. I would like to give them an opportunity--just who you are and your institution.

DR. ZUPPA: Hi. I am Athena Zuppa. I am a pediatric critical-care doctor and a clinical pharmacologist from the Children's Hospital of Philadelphia.

DR. LUQUE: Amneris Luque. I am infectious diseases, board-certified, at the University of Rochester.

DR. HENDRIX: Okay. Thank you both.

Clarifying Questions to Applicant

DR. HENDRIX: Now we are going to open for clarifying questions from the committee for the sponsor. So, again, these are questions to clarify anything that was presented in the presentation and not to get specifically to the questions that you will be asked by FDA at the end of the sessions.

So I will go ahead and open the mikes for your clarifying questions. Dr. Moldanado.

DR. MALDONADO: I am trying to open the file now on the previous document that was sent to us, but I recall that there was another adverse event that I did not see reported here of a child who became floppy and unresponsive after their dose, did not require intervention but was unresponsive for about--I can't recall exactly, 20 to 30 minutes and then actually went on to receive an additional

dose. I would like further clarification about that adverse event.

DR. CILLA: And you would just like a description of that adverse event?

DR. MALDONADO: Yes.

DR. CILLA: I would like to invite Dr. Griffin who will cover that. Oh; I'm sorry. My name is Don Cilla. I will be here helping to clarify the questions that you are asking to clarify and make sure that we get the right experts up on front of the microphone.

DR. GRIFFIN: So we are trying to find the slide. I think you are probably referring to an ALT reported, a preferred term of ALTE?

DR. MALDONADO: I didn't actually see you present it, but I saw it in the background documentation.

DR. GRIFFIN: Okay. We didn't present this but we have it. Slide up.

[Slide.]

This sounds like the case you are referring to. Is that the one?

DR. MALDONADO: That's the one.

DR. GRIFFIN: Further descriptions are on the

slide. It was, as you said, ten minutes from the required dose. It was dose 4 and the child did not require hospitalization. The past history was 28 weeks gestation, had a history of apnea prematurity and, for the event, as you said, there was apnea, bradycardia, floppy, for about ten minutes after the dose, then returned to baseline and was sent home and, as you also mentioned, was re-dosed without recurrence of the event.

DR. MALDONADO: Do you any data on ADA in that patient?

DR. GRIFFIN: I will check. I do not believe there was ADA present in that patient but I will confirm that for you.

DR. HENDRIX: Dr. Murata.

DR. MURATA: I have clarification questions for Slide 31 where you show the forest diagram for Trial 110. Can the sponsor comment on the markedly reduced number of the patients enrolled in the Southern Hemisphere and whether or not specificity that represents the number of sites relative to the other part of the world and whether or not that represents the severity of the RSV seasonal epidemics in those study years.

DR. CILLA: So you are interested in the number of sites as well as the severity of the RSV season specifically to the Southern Hemisphere?

DR. MURATA: Right, and whether those factors reflect the number of patients enrolled in the Southern Hemisphere as it says here 605 versus--which is really 10 percent of the study population.

DR. CILLA: We will invite Dr. Griffin to answer that question.

DR. GRIFFIN: So, if I could just clarify your question so that I can answer appropriately. I am not sure exactly what you are asking. Slide up.

[Slide.]

So, as you mentioned, for this RSV hospitalization endpoint, about 10 percent of the total population, study population, was from the Southern Hemisphere. In regards to severity, we have RSV subtypes circulating in the regions over the years of the study.

What other information would I be able to give you to help answer your question?

DR. MURATA: Maybe I should rephrase the question as follows. Clearly, out of the total patient population of

over 6,000, about 10 percent, or 600, are located within the Southern Hemisphere according to this chart.

DR. GRIFFIN: That's correct.

DR. MURATA: My questions are whether that markedly reduced number in the Southern Hemisphere represent, let's say, the proportion of study sites in the Southern Hemisphere as compared to those in the rest of the world and, two, whether or not there were any differences in the severity of the RSV seasonal epidemic in the Southern Hemisphere versus the Northern Hemisphere during those study years.

DR. GRIFFIN: So, to our knowledge, there was no difference in the severity. Slide on.

[Slide.]

I can show you the subtypes circulating for the regions during those years and 110, as you recall, was during 2004-2005 and 2005-2006. Southern Hemisphere data would be presented for the Year 2004-2005 and you can see it there, that both A and B were circulating during that time and the number of sites--we will have to get that information and get back to you on the number of sites in Southern Hemisphere.

But, as I mentioned in the presentation, we had sites in South America, Chile, Argentina, Brazil and Australia-New Zealand, so not just in one defined location region. They were spread out in the Southern Hemisphere between South America and Australia-New Zealand. But I can get you the number of sites and get back.

Slide off.

DR. HENDRIX: Dr. Clay.

DR. CLAY: Good morning. You stated, or I guess it is in the background material, that motavizumab requires a supplemental dose after any bypass surgeries. In 124, I am wondering how many times did you have to get an additional dose, if any of the subjects had bypass surgery. And then, just a follow up, does palivizumab also require a supplemental dose following bypass surgery?

DR. CILLA: I would ask Dr. Griffin to answer that question.

DR. GRIFFIN: So, yes; that is the recommendation that children who undergo cardiac surgery and require bypass get a replacement dose to get their levels back up to where it was before the bypass procedure.

We have the information, I know, in the CSR. I

have a number but I want to give you the correct number. So let us confirm and I will get back on the number who received a replacement dose after cardiopulmonary bypass in 124. It is for both palivizumab and motavizumab would get a replacement dose.

DR. HENDRIX: Dr. Veltri.

DR. VELTRI: Just two questions related to process. It was noted that the phase-3 study 110 was imitated actually before the end-of-phase-2 meeting. I gather that there weren't any major changes after that end-of-phase-2 meeting in regards to population design or endpoints, that the FDA had concurrence with that trial.

The second thing in process is it was mentioned that the 110 and 124 were pooled data that was prespecified. Was that also with concurrence from the FDA, I gather, because the 124 would not have enough patients in itself to have power for efficacy.

DR. CILLA: I would like to invite Mr. Ross Lobell from our Regulatory Affairs Department to answer the question about the end-of-phase-2 meeting and the agreement about the protocol. And then we will ask Iksung Cho to come up and talk about the pooled data analysis.

MR. LOBELL: So you are correct. The trial did start before the end-of-phase-2 meeting. The end-of-phase-2 meeting did not change the study populations and the approach, we did discuss how we might utilize the CHD population and study effectively within our program.

The statistical analytical plan was prespecified and agreed to with FDA.

DR. CHO: My name is Iksung Cho from MedImmune Statistics Department. The question regarding pooling of the data of the CP110 and CP124, it was not specified in the protocol but it was specified in the statistical analysis plan and that was submitted to the agency prior to unblinding. We received a concurrence from FDA prior to unblinding.

DR. CILLA: I do have a piece of follow-up information on the question about ADA in that subject, and there was no ADA in that subject.

DR. HENDRIX: Dr. Maldonado, you had another question? Then, after that, just so the rest of the panel is clear, I have got Dr. Cargill, Dr. Luque, Dr. Ellenberg and then Dr. Clay.

DR. MALDONADO: Sorry. So going back, when Dr.

Losonsky presented the data on adverse events, it wasn't in the slide but she did say that there were no significant differences in adverse events for TEN, erythema multiforme major. But I recall from the background information that there might have been a difference for erythema multiforme minor. Is that correct, or am I mis-remembering that?

DR. CILLA: I think the simple answer is yes. There were six cases of erythema multiforme minor for motavizumab.

DR. MALDONADO: Okay. And then, I guess, a follow up on that would be, and maybe we can discuss this later, but I assume that you are going to go back and break down the differences, any significant differences, between the children who did have these reactions and those who did not.

DR. CILLA: One second. Let me confer with my colleagues. When you say break down the differences, can you be more specific?

DR. MALDONADO: So, for instance, the children who had erythema multiforme minor, how were they different from the children who did not have erythema multiforme minor since that did seem to be a significant difference.

DR. CILLA: In terms of differences, you are

talking about demographics--

DR. MALDONADO: Demographics, clinical baseline status and the medications that they were on, ADA, et cetera.

DR. LOSONSKY: So I can try to answer your question. Slide on.

[Slide.]

This is the listing of all the cases reported in to us of erythema multiforme and subsequent follow-up questions that gained additional information to try to describe these events.

So there were five events reported in the three main studies with one additional one reported in 127. These events were a variety of severity, as you can see, and a variety of timing, two occurring close to a dosing that were actually treated with antihistamine. There was no blistering or exfoliation which is characteristic of an erythema multiforme major event, short duration. Dosing was to cede in those two children.

It is unclear to us looking at the timing whether this was mischaracterized from an urticarial annularity that has been reported to be confused with erythema multiforme.

Three of the other cases which occurred not temporally associated with dosing had alternative etiologies by the site physicians and several of those were re-dosed without recurrence. The last case in CP177 also had a very short duration and was not treated which is uncharacteristic of an erythema multiforme major.

So we conclude that these events were consistent with erythema multiforme major and a lot of the findings, lack of recurrence with re-dosing, lack of detection of specific ADA, and it was only these two children with the temporally associated events that had anti-drug antibody detected and possible alternative etiologies confound our understanding of these events.

DR. MALDONADO: Thank you. I'm sorry; then, my last question, and I am hoping that we will be able to discuss this later but I want to bring it up now, is that I am hoping that we will see some, again, comparator data between the treatment failures or the children who broke-through disease in the arms compared to those who didn't, so, for instance, those who received palivizumab versus motavizumab and had hospitalizations or events versus those who didn't. What were the differences between them?

DR. CILLA: In other words, looking again similarly to this past prescription on the characteristics of those.

DR. MALDONADO: Right.

DR. CILLA: Is it something you would like to see right now?

DR. MALDONADO: At some point today. I just think it would be important to note for the clinicians in particular what characterizes the high-risk children given that we are going to need to know how to stratify these children based on who is at higher risk for breaking through.

DR. CILLA: Sure. While they are getting that organized, I can provide you feedback on the other questions. Of the Southern Hemisphere sites, there were 33 of those which represent 10 percent of the total number of sites. And then the number of replacement doses in 124, so 121 patients on mota and 136 on pali.

DR. HENDRIX: Dr. Cargill.

DR. CARGILL: I would like to return to the skin-signal question again. We were told during presentation that 17 out of 58 with the ADA had a skin event. I would

like to know if you have analyzed the data particularly given what you were talking about as possible plan for post-approval, that, in the analysis of your data, have you identified any additional or other predictors of those who develop skin manifestations excluding the major skin manifestations, because it seems there is a lot of this.

DR. CILLA: I will ask Dr. Losonsky to provide an answer to that question.

DR. LOSONSKY: Are you talking about skin, itself, or anti-drug antibody?

DR. CARGILL: My question was couched in the context of that, but not just anti-drug antibody. It said that of those 17 out of 58 had that excluding those who have major skin reactions since this signal keeps coming up. Have you looked at the data to see if you have any other predictors of individuals who would go ahead to develop a skin reaction?

DR. LOSONSKY: So Slide S156, please. I'm sorry; 157 first. Slide on.

[Slide.]

So we looked at those demographic factors that might be associated with skin and I am presenting that to

you here. We did find that there was a significant association in non-white-race participants. When we looked at the types of events reported at increased frequency for those, those were the nonspecific rashes which, really, from our point of view are very hard to characterize clinically because of the event terms used and the fact that the docs infrequently treated these events.

But it is possible some of those might be consistent with possible hypersensitivity. Very hard to tell by the event terms.

And then, looking at children with a family history of atopy, again, we saw an increased rate in those children. But, again, they seemed to be confined to the nonspecific rashes.

DR. CARGILL: Thank you.

DR. HENDRIX: Dr. Luque.

DR. LUQUE: You describe a hypersensitivity reaction in 118. Do you have baseline blood pressure in that individual before enrollment into the study?

DR. CILLA: Yes; we do. We have pre-dose blood pressures.

DR. LUQUE: No. I am not referring to the pre-

dose at the time of enrollment. Before that.

DR. CILLA: Yes. They are gathering that information right now.

DR. LOSONSKY: We are going to have to get that slide up for you. We have a pre-dose 1 and 2 blood pressures and they were above 90, you know, in the 100 range. They weren't 125 systolic, which is what happened pre-dose in this child, but they were in the 100 range.

DR. LUQUE: Before the enrollment?

DR. LOSONSKY: Before dose 1 and 2. And dose 3 was the indicator dose for this particular event. Enrollment is the pre-dose-1 blood pressure.

DR. LUQUE: But you commented that, perhaps, that blood pressure was a little higher because of the study participation. So I was wondering what the baseline blood pressure for that child was.

DR. LOSONSKY: Unfortunately, our baseline is the pre-dose-1 blood pressure.

DR. LUQUE: Thank you.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: I have a couple of questions about the dosing discontinuations. For pali, there were multiple

causes of these discontinuations. I wondered whether, if this had been given in a clinical setting, in a clinical setting children getting this, would these have been reasons for dosing discontinuation or was it because this was a double-blind study and they didn't know what they were getting and erring on the side of caution, or following protocol?

DR. CILLA: So the question is were these typical of what you would see in a clinical-practice setting as people were--

DR. ELLENBERG: That's right. Ordinarily if people know that the characteristic were getting pali, would they have discontinued for these variety of reasons.

DR. CILLA: It might be best if we call up one of our external experts to comment on reasons for discontinuation of therapy. Dr. Ramilo, I don't know if you would mind to comment on that.

DR. RAMILO: I think your point is well-taken. In the context of a clinical study, we always act more cautiously. But it is difficult to extrapolate data, what would have happened in clinical practice.

I see your concern, but it is difficult to

interpret out of that how I can--there is no objective data that I can use to give you a precise percentage.

DR. ELLENBERG: My concern is, and I am not sure I am really making a point, but a hypersensitivity reaction that happens shortly after dosing is something that people would likely believe is, in fact, due to the product and might be more apt to stop. Some of these other things, I don't know whether they would be things that, if people observed, they would stop.

So I am trying to use that to interpret the relative rates of dosing discontinuation on the two arms.

DR. RAMILO: The truth is that these are very high-risk babies, most of them premature babies, and they are followed very, very closely in the Neonatology Follow Up Clinic. So these babies are really always followed. They are very fragile, if you want. So we always tend to over-react to things that we do in practice.

DR. ELLENBERG: Okay. Let me ask another question. You showed, I think it was Slide--I can't remember; 51, maybe--where you showed the pattern of discontinuations according to the five doses.

I wondered, there were nine children who were

discontinued from motavizumab and I don't know when they were discontinued or how severe, and I don't know how those discontinuations might have impacted. You had sort of an increase to the second dose and then it went down for the third dose. I kind of wondered whether maybe all the children who were discontinued were discontinued somehow between--before the third dose and then the fourth and fifth dose went up again so maybe there was, in fact, some pattern of increasing the dose.

But it is hard to know without knowing how the discontinuations might have affected that pattern that you showed.

DR. CILLA: So you are asking, for each of the nine patients, whether we know which dose they discontinued following as well as the severity of the event that may have led to their discontinuation.

DR. ELLENBERG: Right, or just a general sense of have you looked at that and how much impact would it have on that pattern that you showed in that slide.

DR. CILLA: Let me just confer with my clinical colleagues for one moment. We don't have that readily available in a slide so they are working on that and we will

save that and get that addressed for you as soon as we can.

DR. ELLENBERG: Okay. Can I ask one more question?

DR. HENDRIX: You can ask one more question.

DR. ELLENBERG: Okay. Thank you. I am not sure you showed us the actual inclusion and exclusion criteria for these studies. Obviously, as you said, these were all sick children, high-risk children. But could you show us the actual exclusion criteria for the CP110. However sick they were, it is not uncommon that the sickest of the sick are often excluded from studies. I am trying to get a sense as to who might have been excluded.

DR. CILLA: So what I am understanding is we don't have that on a slide but are one of you able to talk to that? We will ask someone to come up and talk to those, if that is acceptable.

DR. LOSONSKY: So, for CP110, we used the same inclusion and exclusion criteria that was used in the palivizumab historic trials and that was similar for the Cardiac trial also. So children who had receipt of palivizumab shortly before, and I believe it was three months before dosing, were excluded.

They could receive a dose of palivizumab in a prior season if they were, for example, CLD children who were enrolled up to the age of 2 years and still had ongoing medical management for their CLD which was a criteria. So they had to have ongoing medical management or be recently treated for their CLD. The guidelines for prematurity without CLD was pre-term within or up to 35 weeks gestation.

In terms of other baseline conditions, they were allowed. So a child, for example, a pre-term infant with a neurologic condition would be eligible for enrollment because they are quite common findings in pre-term fragile populations.

Other exclusions--

DR. ELLENBERG: So there were no exclusions on the basis on any kind of level of severity at baseline condition.

DR. LOSONSKY: No; not at all.

DR. HENDRIX: Thank you. At this point, we are going to take a break. Let me just say that we will continue the clarification questions for the sponsor at the conclusion of the FDA's presentation. I have got Drs. Clay, Graham, Freeman, Zuppa and Havens.

So let me just remind you. We will take a 15-minute break. Now it is 10:15. We will reconvene at 10:30. I just want to remind the panel members that is to be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience.

So we will come back to the mikes at 10:30. Thank you.

[Break.]

DR. HENDRIX: Welcome back. We will now proceed with our presentation from the FDA. I would like to remind the public observers at this meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

FDA Presentation

DR. SHAPIRO: Good morning.

[Slide.]

DR. SHAPIRO: I am here to discuss our analysis of the motavizumab BLA.

[Slide.]

In my presentation, I will go over efficacy which will be the overview of the studies CP110, 117 and 124, determination of noninferiority and point analysis of

studies. Also, the safety issues and overall adverse-event profile including deaths and study discontinuations, analysis of acute hypersensitivity events including cases suggestive of anaphylaxis.

[Slide.]

There were five studies, phase 1 and phase 2, to support the BLA. There were two phase 3 studies, CP110 and CP117. Additionally, there was a phase 2 study to expand the indication, CP124, which was those with hemodynamically significant congenital heart disease.

[Slide.]

CP110 study design was a phase 3 randomized double-blind multi-center study of RSV prophylaxis of severe RSV disease in high-risk children. This included premature infants, those with gestational ages less then 35 weeks and less than 6 months of chronological age. It also included chronic lung disease patients less than 24 months of age.

[Slide.]

The endpoints in CP110 included RSV hospitalization which was RSV positivity determined by central real-time RT-PCR assay. The secondary endpoints included medically attended lower-respiratory infections or

MA-LRI caused by RSV, all-cause MA-LRI, frequency and incidence of otitis media and antibiotic use for otitis media and MA-LRI.

In my discussion of the secondary endpoints, I am going to stick primarily to medically attended lower-respiratory-tract infection.

[Slide.]

Now, CP117 was a prevention of RSV disease among Navaho and White Mountain Apache infants. It was a phase 3 randomized double-blind placebo-controlled trial designed to compare motavizumab to placebo. This was randomized 2 to 1 with two of motavizumab to one of placebo.

The primary endpoint was RSV hospitalization with a secondary endpoint of MA-LRI and otitis media.

[Slide.]

CP124 study design; this was an RSV prophylaxis in children with hemodynamically significant congenital heart disease comparing motavizumab to palivizumab. This was a safety trial not powered for efficacy looking at the incidence of RSV hospitalization and the incidence of RSV outpatient medically attended lower-respiratory infection in season 2 as efficacy endpoints, but they were not powered.

In my summary of my efficacy results, I will discuss--in CP110, we will talk about the comparison of motavizumab versus palivizumab, the noninferiority margin determination, primary endpoint and the limitations of the data and sensitivity analysis of the primary endpoint. We will discuss the selected secondary endpoint of the outpatient subset.

In CP117, we will talk about the motavizumab versus placebo looking again at the primary endpoint of RSV hospitalizations. In CP124, we will look at RSV hospitalization.

[Slide.]

Now, discussing the noninferiority margin, we look at a margin of "M." "M" is the degree of inferiority of the test drug as the active control that we wish exclude statistically in the trial. As you can see here, you have a confidence interval around the difference or the ratio of the treatment effect that should not exceed the margin.

As you can see, things are better than the control and worse than the control and you do not want this kind of confidence interval to exceed this margin right here.

[Slide.]

Now, in determining the noninferiority margin, there are two components. There is M1 which ensures that the new drug is better than placebo. This is based on historical data of the effect of the control drug compared to the placebo and this should reflect the uncertainties in the evidence on which the choice is based and should be suitably conservative.

M2 ensures that not too much efficacy is lost. How much efficacy are we willing to lose? We primarily have to use clinical judgment to make this determination. M is the margin used in the trial. This could be the entire effect of the control drug which is M1 or it could be the smaller M2 if there is a need to preserve more than just any of the control drug's effect.

[Slide.]

Now let's go on to the calculation of the margin for Study CP110 for an odds ratio of motavizumab versus palivizumab. As you can see here, looking at the older trial CP018, there was a two-fold decrease in RSV hospitalization with palivizumab versus the control.

Now, taking a look at a 50 percent reduction in the benefit with the ratio of 1.529, we wanted to preserve

about half of the treatment effect. So that gave us a margin of 1.265. So, as long as we do not exceed this margin of 1.265, we can call something noninferior.

[Slide.]

Going on to the efficacy results for CP110, looking at the primary endpoint. As you can see for respiratory hospitalizations, you can see that motavizumab had a decreased number of frequency of RSV hospitalizations at 1.4 percent or 46 RSV respiratory hospitalizations as compared to palivizumab which was 62 which was 1.9 percent. As you can see the odds ratio was 0.73 with a confidence interval of 0.5 to 1.08 falling under the 1.265 noninferiority margin. So we would call this noninferior on the primary analysis.

I should also mention that the difference between the two which we will talk about later is about 16 patients. You can see also there were less total respiratory hospitalizations in which motavizumab had 7.5 percent versus palivizumab's 8.1 percent and that the non-RSV respiratory hospitalizations were comparable.

[Slide.]

Now, going on to this discussion about looking at

geographically the endpoints by region. In the Northern Hemisphere, as you can see, the hospitalizations were comparable between motavizumab and palivizumab. However, in the Southern Hemisphere, they had far fewer hospitalizations for motavizumab as compared to palivizumab, and that was 11 out of 16 patients.

So one could say that the results from the Southern Hemisphere were driving the noninferiority because that made up 11 out of the 16-patient difference.

Also looking at U.S. sites, you can see that we had a hospitalization frequency of 1.9 percent versus 1.8 percent. So it was fairly comparable. And, at non-U.S. sites, you actually saw a decrease in the frequency of hospitalization at 1.1 percent as compared to 1.9 percent for RSV respiratory hospitalizations.

[Slide.]

Now, I would like to go over the issues identified in the first review cycle. Did local RSV testing bias RSV hospitalization decisions?

[Slide.]

In our talking about local RSV testing, motavizumab and palivizumab compete for the F-protein

binding sites of some local RSV assays. They may interfere with local assay results. In vitro studies suggest motavizumab may interfere more than palivizumab.

Also, central testing by real-time RT-PCR in hospitalized patients in CP110 indicates false-negative local test rates twice as high in motavizumab patients as compared to palivizumab. In clinical situations where local RSV tests were used in hospitalization decisions, disparate assay performance could lead to bias.

[Slide.]

This is a schema of how local testing may influence admission decisions. As you know, when you have a patient coming into an ER or into your clinic, not all of them are straightforward admissions. I want to go over that scenario.

So you have someone who comes in, a patient, with concerning respiratory symptoms. Some of them may look so bad that you plan to admit them right away. Many times, you will not obtain a local test because your plan is to admit them. And there may be a few of these that you obtain a local RSV test made, perhaps, for cohorting purposes so that you can decide where in the hospital to place them.

All of these patients that do get admitted, their sample would be sent for RSV real-time RT-PCR to a central lab.

Now, the one that we are most interested in is those where there is uncertainty about admitting. Some physicians, when they are sitting on the fence of saying, well, the symptoms are not so bad. I am kind of managing it in the emergency room, but it is like 10 o'clock in the evening and I am not sure it is going to get worse, maybe obtaining a local test may help.

So what you would have is you would obtain a local RSV test. Our presumption is that if that test was positive that the ER physician is more likely to admit that patient. Of course, that sample, would be sent for RSV real-time RT-PCR to a central lab.

But let's say the local test was negative. Perhaps there was some assay interference. The provider may be likely to observe this patient longer in the E.R. or in the clinic or send them home.

[Slide.]

No, talking about local RSV testing, use of available assays was permitted in the protocols but they

were not officially part of the study protocols. Local testing practice is not systematically documented.

Local testing was conducted in CP110, 124 and 117 and about 65 percent to 75 percent of the hospitalized patients in CP110 had local testing done in close proximity to admission. 11 percent of all these patients with any respiratory event in CP110 had local RSV testing.

In CP110, also, approximately 50 percent of admitting physicians knew the results of local RSV testing prior to admission. Our concern, of course, is there may have been a possible impact on hospitalization decisions for some patients.

[Slide.]

Now, going over the applicant's response to our Complete Response Letter, they conducted a review of the case-report forms and source documents of patients from CP110 and CP117 to document local testing practices of all respiratory hospitalizations, all outpatient MA-LRI's including those that had RSV samples collected, not collected or collected but not run, most outpatient upper-respiratory illness, and they also ran previously banked not processed samples for central analysis.

They also did a sensitivity analysis to gauge the potential bias of local testing practices on the primary endpoint.

[Slide.]

Let's talk about the sensitivity analysis in CP110. I wanted to give two examples from the multiple sensitivity analysis that we did confirm. They were to evaluate the effects of possible bias in hospital admissions due to false-negative local RSV tests, tests that might have been false negative. And they did an analysis that imputes; that would be adding additional RSV hospitalizations based on all known false-negative local test results and a proportion of potentially false-negative tests.

These analyses attempted to correct for patients that might have been hospitalized but were not because of a local test that was falsely negative and could have influenced the clinical decision not to hospitalize.

[Slide.]

Let's go over the first example using lower-respiratory illnesses. Basically, they added all outpatients with medically attended lower-respiratory illnesses known to have a false-negative local test. They

also added outpatients with medically attended lower-respiratory illness who could have had a false-negative test based on a negative or unknown local test and no central test results.

Then a proportion was added based on the probability estimation using a model subject with a known local and central test result.

As you can see here, looking at these potential false-negatives for both motavizumab and palivizumab, they estimated additional patients that were possibly true RSV positive. That was eight for motavizumab and two for palivizumab. They added those eight or two to the known false-negative local test. When they added them up, for motavizumab, they had a total of 13 patients added to the RSV hospitalizations while they added seven for palivizumab.

Using the analysis with these added hospitalizations, noninferiority was maintained with an odds ratio of 0.85 with a confidence interval of 0.6 to 1.20 which fell under the noninferiority margin of 1.265.

[Slide.]

Now, going on to our second example where they looked at any respiratory illnesses, they added all

outpatients with any medically attended respiratory illness known to have a false-negative local test. They added outpatients with any medically attended respiratory illness who could have had a false-negative test based on negative or unknown local test and no central test.

Also, the proportion was added based on a probability estimation using a model subject with known local and central test results. So, again, we do a similar analysis looking at the potential false-negatives for motavizumab and palivizumab and then estimating additional patients with two RSV positives. So there were 37 for motavizumab, 11 for palivizumab.

They took the known false-negative local tests and added them and they added a total of 50 additional RSV hospitalizations for motavizumab and 26 for palivizumab. So, as part of this modeling, they did a calculation of the noninferiority. Noninferiority was not maintained because the odds ratio was 1.09 with a confidence interval of 0.81 to 1.46 which exceeds the noninferiority margin of 1.265.

[Slide.]

Moving on now to CP110 secondary endpoint in the outpatient study subset looking at MA-LRI, we have for

motavizumab a 2 percent frequency of MA-LRI as compared to palivizumab with a 3.9 percent.

Looking at any MA-LRI including those that are non-RSV, the frequency for motavizumab was 19.2 percent which was comparable to that of palivizumab at 21.2 percent.

[Slide.]

Limitations of the secondary endpoint for outpatient MA-LRI. Endpoints were only evaluated in a subset of study sites. There was a substantial rate of missing data. Motavizumab had 19 percent and palivizumab had 18 percent due to missing RSV samples. The missing data might result in a reduction of motavizumab's estimate of benefit over palivizumab for preventing RSV MA-LRI.

[Slide.]

Now, going on to CP117, which is the study in Native American children of motavizumab versus placebo, looking at the intent-to-treat population, looking at RSV hospitalizations, as you can see, the frequency of RSV hospitalization, the motavizumab arm, was 1.4 percent versus placebo which was 8.3 percent.

As you can see with the odds ratio with 0.16 that motavizumab was superior to placebo. Respiratory

hospitalizations were also reduced at 9 percent as compared to 13.6 percent for placebo.

One thing of note was non-RSV hospitalizations, we had a 7.6 percent in motavizumab as compared to 5.3 percent in placebo. This was a little different than what we had seen in other studies so this may indicate that the Native American children may be a different population and there may be other study effects involved.

[Slide.]

Going on to CP124, they are studying hemodynamically significant congenital heart disease. Looking at RSV hospitalization, for motavizumab, the frequency was 1.9 percent versus palivizumab at 2.6 percent.

[Slide.]

Now to summarize for efficacy, motavizumab met the noninferiority criteria for the primary analysis in CP110. However, there were limitations. These limitations include local test results might have influenced respiratory hospitalization admissions. Given the low event rate, these results are sensitive to misclassification of a few events.

Also the applicant's sensitivity analysis may be insufficient to rule out an important impact of local

testing on the primary endpoint because of uncertainty in capturing all local test results.

[Slide.]

Also, in CP110, the secondary endpoint, there were fewer RSV MA-LRI events in subjects who received motavizumab as compared to palivizumab.

In CP124, although underpowered for efficacy, primary endpoint results were numerically consistent with those observed in CP110. In CP117, in Native American children, subjects receiving motavizumab had statistically fewer RSV hospitalizations than subjects receiving placebo.

[Slide.]

Now, going on to my safety discussion. I want to mention that the applicant responded to our concerns about sudden infant death syndrome, apparent life-threatening events, neurological adverse events and neutropenia.

Hypersensitivity was identified in more patients who received motavizumab than palivizumab. And there were also cases suggestive of anaphylaxis also identified in patients who received motavizumab.

[Slide.]

Going over to the adverse events looking at CP110

and 124, because they were slightly more comparable populations, as you can see overall, looking at the adverse-event rate frequencies for motavizumab versus palivizumab, for CP110 they are similar. The same is true for CP124. And also, looking at the higher grades looking from both arms across each other, they do have similar rates although I have to mention that, in CP124, being a study of a more fragile population, those with hemodynamically significant congenital heart disease, we did see a higher frequency of grade 3 and grade 4 adverse events and serious adverse events.

This is probably that a lot of these patients had undergone surgery and had other reasons because of their underlying illness to have a higher frequency.

[Slide.]

Now, going on to deaths, looking at the three studies under discussion, in CP110, as you could see, there were eight deaths as compared to four with a frequency of 0.2 versus 0.1 percent.

In CP124, there were nine deaths in the motavizumab arm as compared to 10 in the palivizumab arm. For CP117, there were three. In placebo, there were two but

this was at a 2-to-1 ratio because there were two of motavizumab and one of placebo.

But, looking overall at death, the frequency for motavizumab was 0.4 percent as compared to palivizumab which had a similar frequency and we also had a similar frequency in the placebo.

[Slide.]

Now, causes of death in CP110. As mentioned earlier, there were more SIDS deaths in motavizumab as compared to palivizumab. And, in the motavizumab arm, we had two deaths due to pulmonary hypersensitivity, one to pneumonia and one to aspiration. In addition, for palivizumab, there was one due to airway obstruction and one hemodynamically uremic syndrome that was after an RSV infection.

[Slide.]

Now, in CP124, as mentioned, this is a study in cardiac patients. In motavizumab, there were four sudden deaths which also, using the same category, four sudden deaths in the palivizumab arm.

Continuing on with motavizumab, there were two post-surgery cardiac deaths, two due to sepsis and one due

to Tetralogy of Fallot cris with cyanosis. Going on with palivizumab, there were two cardiac arrests, one considered slightly coded differently as one cardiorespiratory event, one due to pulmonary atresia, one due to pneumonia and one due to bronchiolitis.

But I do want to mention that the palivizumab arm had a higher proportion of patients with cyanotic heart disease and uncontrolled heart failure as compared motavizumab patients at enrollment.

[Slide.]

Now, in CP117, in the motavizumab arm, we had one due to sepsis and one other due to head injuries. In the placebo, there was one co-sleeping death and one that was gastroenteritis-related.

[Slide.]

Now, going on to adverse events leading to discontinuations. In CP110, there were 13 discontinuations in the motavizumab arm as compared to 10 in the palivizumab arm. And then, going on to CP124, there were none in the motavizumab arm but one with palivizumab.

Now, combining them together, we get 13--that is combining CP110 and 124 together, we get 13 versus 11 which

has a somewhat comparable frequency combining these two studies together. With CP117, we had three discontinuations versus zero for the placebo.

[Slide.]

Now, going on to some of the reasons for the investigator-initiated discontinuations for CP110 and 124, as mentioned earlier, for combining these two, that there were nine discontinuations in motavizumab in both studies compared to one in palivizumab. All these nine came from CP110. There was one neurological-related discontinuation for motavizumab, three for palivizumab.

For apparent life-threatening events, there was one event in the palivizumab arm that led to discontinuation. For pulmonary events, there was one for motavizumab versus four in palivizumab. For others, there were two and two which, for motavizumab, the two others included pyrexia and bacterial abscess. For palivizumab, HUS and neutropenia.

Looking at the total, we have 13 versus 11.

[Slide.]

Now moving on to acute hypersensitivity reactions with onsets with 48 hours, we took a conservative approach

looking at urticarial-type and allergic-rash events and comparing them across the three studies looking at motavizumab versus palivizumab and also looking at motavizumab versus placebo.

As you can see, looking at first at urticarial-type events that motavizumab had three times more urticaria in CP110 than palivizumab did. This three-fold--you know, this is about two-and-a-half-fold--holds up for CP124 motavizumab versus palivizumab.

When you combine these two together, looking again at motavizumab versus palivizumab, we are getting again about a three-fold increase of urticarial and allergic rash in motavizumab versus palivizumab. It is similarly true with CP124.

Now, in CP117, we had about a 1 percent rate comparing urticarial and allergic rash types events versus none for placebo.

[Slide.]

Now, I wanted to talk about differences in the severity of hypersensitivity reactions in CP110. Again, these are acute hypersensitivity skin reactions. As you can see for motavizumab, more than half of the urticarial

adverse events were grade 2 and grade 3 as compared to just grade 1 for palivizumab.

Also, the same is true for allergic rash in that, even though most of them were grade 1, we still had some grade 2 and grade 3 with none for palivizumab. So, again, you can tell from this that motavizumab has adverse events of higher severity than those of palivizumab when we are talking about skin hypersensitivity reactions.

[Slide.]

Now, talking about the timing of hypersensitivity reactions in relation to dose, these, again, are the acute hypersensitivity reactions. As you can see, for both motavizumab and palivizumab, most of the reactions occurred second dose and after.

From this, what we can say is that there is really no predicting exactly when these adverse events can occur because, as you are seeing, you even see events after dose 5. So I think, just because we see the first and second dose and did not have a reaction does not mean that you are not going to have a reaction in the later dose.

[Slide.]

Going on to the high-grade hypersensitivity

events, and these are the grade 3/grade 4 or serious specific skin hypersensitivity reactions that occurred within two days of dosing.

I want to mention, looking across CP110, 124, 117, 118 and 127, there were 19 levels grade 3/grade 4 or serious hypersensitivity events versus zero for palivizumab. There was also, in CP124, CP117 and CP118, one case each that was suggestive of anaphylaxis.

I also wanted to mention that, of these 19, nine of the hypersensitivity reactions occurred on the fifth dose. Another nine occurred with causing discontinuation of drug before the fifth dose. And there was one of these 19 that continued all the way to the fifth dose.

Getting back to what was discussed about erythema multiforme, there was a case of erythema multiforme minor in CP110 that led to discontinuation and there was also one in CP127.

[Slide.]

Now, going to the timing of high-grade hypersensitivity events for motavizumab, we looked at the spectrum within the first two days. As you can see, we had a total of eight that occurred within one hour of dosing.

So these are the patients that you would typically dose and monitor for an hour in your clinic prior to be sending home.

And then, looking afterwards, we had patients that had--the remaining 11 had one set occurred after one hour, even going up to 36 hours after dosing having a grade 3 hypersensitivity event which, at that point, one would not be expected to be at clinic at that time.

[Slide.]

Now before I talk about the cases suggestive of anaphylaxis, I want to go over the definition of anaphylaxis. This is based on the Second National Institute of Allergy and Infectious Disease and the Food, Allergy and Anaphylaxis Network Symposia that occurred in July 2005.

The symposia was held to help come up with a better definition of anaphylaxis and to also make recommendations for treatment decisions.

Anaphylaxis was defined as having any one of these following three criteria: one, acute onset involving skin, mucosa or both and at least one of the following; respiratory compromise, decreased blood pressure or end-organ dysfunction; two, two or more that occur rapidly after exposure including involvement of the skin, mucosal tissue

or respiratory compromise, decreased blood pressure or associated symptoms, and persistent G.I. symptoms; and the third, decreased blood pressure after exposure to a known allergen.

[Slide.]

I do want to make some additional points about the definition. This definition does not require the presence of shock nor the administration of epinephrine or I.V. resuscitation to classify an event as anaphylaxis. Anaphylaxis reactions can vary in severity from mild to cardiovascular shock.

Also, anaphylaxis is potentially life-threatening, by virtue of its multi-system involvement and inherent unpredictability. Also, the natural course of anaphylaxis is not fully understood.

[Slide.]

Now, going over our analysis of cases suggestive of anaphylaxis.

[Slide.]

The first case which was in discussion previous by the applicant is in CP118. This is a 16-month-old, 34 gestational age, who had a history of atopic dermatitis who

did well with the first two doses of motavizumab. Fifteen minutes after her third dose, she developed a dry cough, periorbital erythema, lesions on her back and neck and mild palpebral edema.

Her blood pressure dropped from 121 over 72 pre-dose to 75 over 50 30 minutes post dose. There was no prior hypertension with doses 1 and 2. In these prior doses, the child has systolic blood pressure greater than 100 mm Hg. This patient was treated with antihistamine. Approximately 15 minutes later, the patient's cough and palpebral edema and some skin lesions decreased.

There were new lesions around the nose and mouth. This patient was given 10 mg of oral prednisone and 30 minutes later, there was decrease in the facial lesions with continued improvement. The event resolved the same day, sent home on a five-day treatment of antihistamine and prednisone and the investigator coded this adverse event as grade 4, life-threatening.

[Slide.]

Now, going on to the second case, this occurred in CP124. This was a 14-month-old female who had basically 42 weeks gestational age with ASD and weight decreased less

than the 10th percentile who had no prior history of drug allergies.

One hour after the fifth dose of motavizumab, she developed severe urticaria on her face, torso and legs with edema on her cheeks and hoarseness. Her vital signs remained normal. This patient was given hydrocortisone intravenously followed by oral antihistamine and calcium.

Two and a half hours after dose, her urticaria and edema on the cheeks had disappeared. This patient was observed and subsequently released in good condition. The investigator assessed this as a grade 3 hypersensitivity.

[Slide.]

Going on to the third case in CP117, this is a 6-month-old Native American female with a history of reactive airway disease, erythematous maculopapular rash in the past. Within an hour following dose 5, this patient experienced swelling of the eyes, face and fingers, erythema of the face and arms and mild wheezing in the right upper lobe.

This patient was treated with IM Benadryl and solumedrol, albuterol and inhaled steroids. This event resolved the same day. The investigator assessed this event as a grade 3 hypersensitivity.

[Slide.]

Now, I wanted to mention two additional cases of grade 3 events of concern. One thing was that, in CP110 and CP117, as compared to CP124 and 118, the blood pressure was not recorded in the study since it was not required in the protocol.

Now, with the first patient in CP110, there was one grade 3 urticarial event that had tachycardia going from 153 pre-dose to 192 afterwards. Also, in CP117, there was another patient with a grade 3 hypersensitivity urticarial event who had tachycardia with a heart rate going up to 186 and tachypnea.

[Slide.]

Going on to discussion of the anti-drug antibodies to motavizumab and skin hypersensitivity reactions, as we noticed, about 1.8 percent of the patients had an anti-drug antibody detected to motavizumab. Of these, about a third had a hypersensitivity event of interest.

Looking at the 1.8 percent who had the anti-drug antibody, about 10 percent had a grade 3 or above, or a serious, adverse event. 8 percent of the patients with the anti-drug antibody had a discontinuation due to an adverse

event.

Looking at the relative risk of a skin hypersensitivity reaction in those with anti-drug antibody, as you can notice, for those that had a grade 3 or greater adverse event or serious adverse event, the presence of an anti-drug antibody puts you at a 26-fold risk of having this level of a hypersensitivity event.

[Slide.]

Now, to summarize, the overall safety profile of motavizumab and palivizumab were similar in CP110 and 124. However, motavizumab has an increased frequency of hypersensitivity reactions compared to palivizumab including cases suggestive of anaphylaxis.

Safety data from CP117 only reflects the adverse-event profile of motavizumab in Native Americans.

[Slide.]

Motavizumab had three cases per 5,360 patients exposed suggestive of anaphylaxis with a potential rate of 56 per 100,000 patients exposed. Motavizumab has had at least a three-fold increase in severe skin hypersensitivity reactions as compared to palivizumab.

In CP110, the majority of study-related

discontinuations for motavizumab were due to hypersensitivity reactions. In CP110, there were no hypersensitivity-related discontinuations for palivizumab but also noting that, in CP124, there was one discontinuation for palivizumab.

[Slide.]

Also, there were no cases of anaphylaxis in the original palivizumab database and in the motavizumab development program in patients who had received palivizumab.

In 12 years since approval, experts estimate there were approximately 1.2 million patients dosed with palivizumab. We have identified ten postmarketing cases of anaphylaxis for palivizumab that were spontaneously reported to the AERS database. Although I want to emphasize that the AERS database is not suitable for calculating adverse-event incidence due to the nature of the spontaneous reporting.

Also, there is a warning for anaphylaxis that appears in palivizumab's label. Also, palivizumab is commonly administered at home or in a clinic setting and there have been multiple studies of palivizumab to support the safety of home administration by health professionals.

[Slide.]

Now, to conclude with the risk/benefit. Motavizumab has an increased frequency and greater severity of hypersensitivity reactions including at three cases suggestive of anaphylaxis compared to palivizumab.

Motavizumab met the noninferiority criteria for RSV hospitalizations in the primary analysis in CP110 and was superior to placebo in CP117. However, there were limitations to CP110. The results were sensitive to misclassification and also there is a need to consider the impact of local testing procedures.

Thank you.

Clarifying Questions for FDA and Applicant

DR. HENDRIX: We are going to take clarifying questions for the FDA now since that is fresh. Then we will come back to the clarifying questions that remain for the sponsor. Dr. Zuppa.

DR. ZUPPA: Thank you for that presentation. With regards to Slide 39, it seems that the denominator is the number of events or hypersensitivity reactions for both groups. I was just wondering if these 38 events happened in 38 different patients or subjects or 15 different subjects.

If the event happened in one subject, was that subject predisposed to having more events?

DR. SHAPIRO: There were subjects who had a prior event who were re-dosed and had another event especially for those that had the higher grade. Most of them got discontinued but there were a few patients that were continued on for the finishing of their dosing. The numbers here you are looking at are actual patients rather than events.

DR. ZUPPA: They're patients.

DR. SHAPIRO: They are patients, out of 38 patients.

DR. HENDRIX: Dr. Clay.

DR. CLAY: My question is on Slide No. 33, you mentioned that there is a higher proportion of patients with heart disease and uncontrolled heart failure compared to motavizumab. Was there a statistically significant difference between that and the comparator groups or not?

DR. SHAPIRO: When looking at the enrollment which was after randomization, we saw a difference that appeared to be larger than one would expect from just randomization. Just these things panned out, that when you do a

randomization, that we saw these differences. The reason why we highlighted them was that these patients could have more severe adverse events and might create an imbalance. That is why we pointed it out, just to make the committee and others aware that this may influence differences.

DR. CLAY: But there wasn't a statistically significant difference between the groups in those characteristics.

DR. SHAPIRO: No. It was not statistically significant.

DR. CLAY: Thank you.

DR. HENDRIX: Dr. Roland.

DR. ROLAND: So you describe the geographic variability and the efficacy outcome but I don't remember any speculation about what might have caused that or any concerns that you wanted to raise. So I wanted you to address that.

Also, was there any geographic variability in any of the safety outcomes?

DR. SHAPIRO: So, specifically talking about the geographic, correct? Let's go back to Slide 13. Well, one thing I want to point out about the Southern Hemisphere;

they had a higher attack rate of RSV. There was also an increased use of local testing. Those are things that we noticed when we reviewed the data.

These were things that stood out and we wanted to point out to committee that there were these differences that we noted, although we do not have a direct explanation of why these differences occurred.

DR. STRADER: I wanted to piggyback on that. So you are saying that the patients from the Southern Hemisphere had more adverse events.

DR. SHAPIRO: No, no. The Southern Hemisphere, when we are talking about Southern Hemisphere, they had a higher--when I said attack rate, I meant increased incidence of RSV hospitalization in the Southern Hemisphere as compared to the Northern Hemisphere. That is what I meant; not adverse events, but attack rate for RSV.

DR. STRADER: Okay.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: You stress the possible bias associated with the failure to capture all local test results and then questioned the sensitivity analysis that the sponsor had made that it may not have counted because

you don't know what you don't know, what you are missing.

Did you do any further sensitivity analyses to possibly quantify the magnitude of this because I don't have a sense for how much worse it could be.

DR. SHAPIRO: Primarily, we used the applicant's sensitivity analysis including the one example I gave which was much more conservative. We did not do any additional--we basically confirmed what the applicant had given us.

DR. ELLENBERG: Another question.

DR. HENDRIX: Yes.

DR. ELLENBERG: And this is related to a question I asked the sponsor. There were a lot of adverse events reported in the study and you have appropriately reported all of adverse events that occurred without attribution. But the hypersensitivity reactions are ones that that would be most likely, one would think, attributable to the product.

Have you done an analysis of adverse events that you thought were more likely attributable to drug and how that compares because, overall, the adverse events were similar. But it may be that the vast majority of those adverse events were things due to the disease and had

nothing to do with the drug.

DR. SHAPIRO: Well, in the way of looking at--as the applicant and we had mentioned, let's go on to just discontinuations to give you an example of profile. Let's go on to my backup Slide 5.

[Slide.]

Just to give you--you were asking about other adverse events. These are what the study site investigators considered for discontinuation. As you can see, with neurologic, there were more in palivizumab. There was a nystagmus, lethargy and convulsion adverse events that led to discontinuation as compared to one for motavizumab.

But I should say that part of what we saw not only expanding beyond these discontinuations is that we also saw that there was an imbalance in neurological adverse events in total with motavizumab appearing to have more than palivizumab.

But this was actually go on to Slide 6 of the backup, the next one.

[Slide.]

Looking at other adverse events, trying to get a handle of whether motavizumab had a higher degree of

neurological adverse events, as you can see, for seizures, palivizumab had a higher frequency. But if you look at other things such as activation increase, an example being restlessness, again you saw more in palivizumab.

But then switch the category to activation decrease which is more of lethargy, you saw more in motavizumab as compared to pali. That was also true for increased motor events which would be like hypertonia, at 1.4 percent, and hypotonia at 0.5 percent.

So, when we looked at the adverse events that could be drug-related, we looked back and forth. As part of our complete response, we asked the applicant to analyze neurological. We asked them to look at SIDS and apparently life-threatening events to try to see what these imbalances were for the neurological adverse events and for the SIDS.

They had an external consultant that went over these events and the conclusion was that, based on the populations that we were looking at, the frequency of adverse events we saw on the whole were not significant for that population.

So, yes; we did quite a back-and-forth on trying to identify what things were different.

DR. HENDRIX: Dr. Havens.

DR. HAVENS: There are a couple of questions I have, one on Slide 37 which goes to this issue of trying to sort out, perhaps, more specific adverse events that would be hypersensitivity and related to administration of the drug. So this is hypersensitivity within 48 hours.

And then carrying that through, was there any analysis that you did that showed a statistically significant difference in hypersensitivity when you focused on just these possible allergic reactions within 48 hours which would be the most concerning?

DR. SHAPIRO: So you mean of the 19 ones, the grade 3-grade 4, those were the ones that I focused on on Slide 40. Basically, the most severe ones go into 40 right here.

With 19 versus 0, if you do the statistics on it, we come out with about a three-fold difference because you have to look at the 95 percent confidence interval of your difference because you are doing 19 versus 0. Dr. Lei Nei went over and did the calculations for me, and we believe this 19 versus 0 is quite significant.

Lei, is 3.2 considered about right, 3.2 fold?

DR. NEI: Yes. So, originally, if you look at the 19 versus 0, of course, the p-value is less than 0.000000. So, if you have a high confidence level to say a three-fold change--so if I cut 19 to 6, it is more than three-fold in motavizumab. So the 6 out of this 5,620 compared to 0 out of 3,900 for the palivizumab group, this still is going to be at the level 0.05. So we have 95 percent confidence to say it is at least a three-fold change. That is the analysis I have done.

DR. HAVENS: Thanks. And then, on Slide 49, sort of a similar question about the statistical analysis. That is very helpful, by the way. So, statistically, you think that there is at least a three-fold increase in what we might agree would be serious hypersensitivity within 48 hours.

And then, in the relationship of the relationship of the anti-drug antibodies and skin hypersensitivity reactions, the relative risks there look high but there are no confidence intervals for these. Are any of those statistically significant or not? This is your Slide 49.

DR. SHAPIRO: I understand.

DR. HAVENS: I am trying to relate the biologic

plausibility argument here.

DR. SHAPIRO: I don't think we had requested a statistical analysis of the anti-drug antibody and the relative risk. These are basically relative risk based on taking the comparison of those patients--the frequency of what we saw in those patients that were detected over those that were not detected.

If you look just--because you are basically taking the frequency, let's say, for the one that is 27-fold, you are taking 8 over 75 and comparing that to 15 over 4,137 to say what is your risk if you had a anti-drug antibody to having this reaction as compared to the other.

For the purposes of this meeting, I did not have a statistical analysis of this relative risk that I put up.

DR. RALSTON: This question refers to your Slide 13, the CP110. You point out the heterogeneity in the Southern Hemisphere data, and that is apparent in the sponsor's slide as well.

Is it appropriate, or did you consider--you know, if you were considering each of these populations as a separate study in a meta-analysis, you would immediately exclude the Southern Hemisphere data in a sensitivity

analysis. I mean, can you do that? And would that mean that the data would then no longer stay below the noninferiority limit.

DR. SHAPIRO: Well, we actually looked at that. Lei, you did the exclusion, taking out the Southern Hemisphere, how it would look.

DR. NEI: Yes. If you exclude the Southern Hemisphere to noninferiority, you will fail. Even consider the Southern Hemisphere only has 9 percent of the data and the Northern Hemisphere, you have 91 percent of the data. So if you just consider the 91 percent of the data, noninferiority fails.

But somebody will question that there is only 91 percent of the data. So I did include--artificially impute this data into 100 percent, and the noninferiority still fails.

So one word; if you only include the Northern Hemisphere, the noninferiority will fail.

DR. STRADER: Is it valid to do that? Why would you separate the patients into Northern Hemisphere and Southern Hemisphere? It is almost like brown eyes and blue eyes. Why are we doing this? It almost seems it is

contrived in a way to try to find a difference that may not necessarily make much of a difference.

DR. SHAPIRO: Part of this is our regulations. We are supposed to approve drugs for the U.S. population. And so part of our analysis that we always do is to look at U.S. versus non-U.S. populations to see if they are--I understand that you could say that the disease may be similar in different places in the world and we use studies from other countries to support drug approval or drug product licensure in this country.

But, in our analysis, it just stood out because part of the decision-making process is is there something different--let's say, in the U.S., we have different hospitalization practices. We probably use local testing at a different frequency.

I think, in this country, there probably is a tendency to keep patients out of the hospital more for one reason and another. These are all suppositions. I don't have any numbers to back this up, but these are thoughts that, when we thought through why there may be differences.

But if you ask me directly if it is disease-related, I don't have any direct explanation for it.

DR. STRADER: So then those differences may be related to differences in style with respect to hospitalization and physician discretion, et cetera, and not necessarily due to the drug because, the way it is presented, it appears as though it is due to the drug.

If you remove the patients from the Southern Hemisphere, then the drug does not work. It is not noninferior in the United States but that may not be necessarily drug-related as related to the style of admitting patients and physician discretion in the U.S.; is that correct?

DR. SHAPIRO: I think the way you look at it is a drug may have activity but how you study the drug and how the study is carried out does reflect on your primary endpoint.

Let's say you are able to keep most of your patients out of the hospital in this country and let's say there was almost--varied levels or very small numbers. It would be very hard if you had a very small number of hospitalizations to show any effect.

Now, in an area where you have a higher degree of RSV disease and you are more likely to hospitalize the

patient, it is easier to compare to two products, to compare motavizumab versus palivizumab. So these practices do reflect--and how the protocol is designed, will enable you to characterize the activity, or differences in activity, shall I say.

DR. HENDRIX: Dr. Havens, do you have a follow-up to this question?

DR. HAVENS: Yes; just a specific follow up to this. So one is, in the palivizumab arm--still on Slide 13, the hospitalization rate was 4.2 percent in the Southern Hemisphere versus 1.6 percent in palivizumab. So that would go to what you are talking about as a practice difference.

Did you do an analysis to look at the disease severity in patients who were hospitalized in the Southern Hemisphere versus the Northern Hemisphere just in the palivizumab arm which would go to your theoretical statement that there is a practice difference in hospitalization. Sicker patients are sent home or something like that.

That would be one approach to that that could get to that issue. And then the other issue that is, perhaps, of more concern is an issue of biology. The sponsor showed us a quick slide suggesting that there is more RSV-B in the

Southern Hemisphere in the year in which it was done.

It seems like motavizumab is better for B than might be for A, so it had similar protective effect for A so would not have reached a noninferiority margin for A but did look like it was better for B. So this could be an issue of biology in terms of--so I don't know if you stratified by RSV-A or B.

So those are two related questions to this issue of geographic variability.

DR. SHAPIRO: Okay. The other thing is it is also a question of the testing and the testing showed more RSV-B. So you have to look at the components. When I tried to get RSV-A versus B looking at patterns over time, looking at like reports out of Australia, over time, if you look at the amount of A and B, they are fairly comparable.

So maybe a particular year, you may get more B than A.

The other thing is we know that the problems with local testing, detection of the particular RSV isolate, is also another issue when you use local testing, that you may be able to more differentially detect one versus the other, RSV-A versus B when local testing is used to help you in

your admissions decisions.

DR. HENDRIX: Dr. Maldonado, you have a follow-up, but just so the rest of you know, I have got Dr. Graham, Veltri and Roland to follow.

DR. MALDONADO: I have two follow-up questions. The first one had to do, going back from the beginning of your presentation of Slide 13, regarding the difference. The first point is that serotype B may not always be as severe. So did you adjust for severity--in your analysis of looking at circulation?

I mean, I think that is another issue, is looking at severity of B versus A and the likelihood of admission. So it may be not only a biological issue but a geographic issue in terms of more likely to be hospitalized as well as just testing differences.

So I think that is an important consideration, number one.

The second question is when you brought up--I am a little confused about the terminology because you interchange U.S. and Northern Hemisphere. I am not quite sure--I need to understand whether you are talking just U.S. or Northern Hemisphere when you are looking at the

comparison and the failure of the noninferiority.

DR. SHAPIRO: Well, what we are showing here, we looked at Northern Hemisphere versus Southern Hemisphere. When I talked about the U.S., I just gave you an idea from the regulatory standpoint. We are asked to look at U.S. versus non-U.S.

We, basically, for this also broke--you know, as you saw here, broke it apart to Northern Hemisphere versus Southern Hemisphere. And we just included U.S. versus non-U.S. sites as to put it in context.

DR. RALSTON: So the U.S. data is what you used to determine noninferiority differences, then, on Slide 13. So you say 1.9 versus 1.8 and noninferiority is not reached in that situation; is that correct?

DR. SHAPIRO: That's correct.

DR. MALDONADO: Okay. And then, in terms of the first question, going back to serotype B, because that is, I think, a critical issue because that is apples and oranges. If you are comparing the circulation of predominantly B in an area which is less severe in general, then it may counterbalance the testing practices in some way. So I am not quite sure how I would interpret that data.

DR. SHAPIRO: I think the point of showing this data was more to highlight the things that did not make sense. I think a lot of what we show here is that problems that we identified in the review and that we tried to make sense of and do a statistical analysis by asking the sponsor to look at the frequency of A versus B, and we asked them to do this.

A lot of this came out in the Complete Response Letter. So, like I said, the purpose of this slide is just to highlight things that we saw that added some question. I understand that trying to put your hand on exactly why they are different, it is multifactorial and there are many things involved.

I agree. It could be the virus or it is RSV-A versus RSV-B. It can also be local practices and local testing or the E.R. or clinic person making their decisions for hospitalization.

So I think there is a lot to it. As I mentioned, we do these calculations or estimations as part of our thing when we are approving or licensing a product for the U.S. We just want to point this out as an interesting difference that we saw.

DR. HENDRIX: As we go on, let me just remind you, these are clarifying questions for the data that was presented. Some of these started to get into more discussion and we are going to have time this afternoon to do that when we get to the questions.

But, please, ask your questions. So now Dr. Graham.

DR. GRAHAM: This is a clarification about the Southern Hemisphere again. So did you say that you thought that the local RSV test positive was a greater factor in hospitalization in the Southern Hemisphere or did you just say that the hospitalization practices in general were different?

DR. SHAPIRO: A lot of this is taking the data as best we can. We do know that practices are different in the way of RSV--I didn't say local RSV positive so much as we know that there is a higher degree of local testing being done in the Southern Hemisphere, and that may impact, basically, because we are concerned about possible interference or bias with local testing.

DR. GRAHAM: But you did not say that local testing positive would lead to hospitalization at a higher

rate than local testing negative.

DR. SHAPIRO: I was not saying that.

DR. GRAHAM: Okay.

DR. HENDRIX: Dr. Veltri.

DR. VELTRI: I have two questions. One relates to this regional disparity which is very common, actually, when you do these multi-center, multi-national trial. And the second question relates to, perhaps, trying to get a better understanding of the hypersensitivity anaphylaxis risk with this drug.

Regarding the regional discordances, in the original palivizumab filing, were there any discrepancies regionally, U.S., in particular, versus others or was that really more of an Northern Hemisphere trial--just to get a sense of this.

DR. SHAPIRO: If I recall correctly, 018 was primarily a Northern Hemisphere

DR. TAUBER: There were just three countries involved in the original study, the United States, Canada and the United Kingdom.

DR. VELTRI: Okay. Because, as I said before, we see this a lot. We do these analyses, but then we are

trying to explain something which has a lot of variables in it. So I am not sure what it all means.

Secondly, in regards to the hypersensitivity anaphylaxis risk, you mentioned that, in the current database and the previous database with the previously approved drug, there were no cases of anaphylaxis.

In Slide 40, when you look at high-grade hypersensitivity , one is truck by, obviously, absolutely zero cases in the palivizumab. If you looked at the palivizumab experience rather than true anaphylaxis, looking at high-grade hypersensitivity before approval, were there any signals there along the same type of guidelines and, of the cases that have been described in the pharmacovigilance, even though there are confounders and who knows what it means, you said there were ten, were any fatal?

DR. SHAPIRO: Yes. There were ones that were fatal there. There were a number of them, actually. I have that data with me. There was one out of that that was fatal. I have all the cases right here that I am looking at.

DR. VELTRI: Could you glean anything if you classified, and you may not have done it, looking at high-

grade hypersensitivity in the control database--in other words, trying to get a sense, even though it is rare, once it is out there in the market, are there any signals there?

DR. SHAPIRO: Our overall sense from our review, and this is more of a gestalt, is that, overall, for palivizumab, that these high-grade hypersensitivity events are quite infrequent and they are not very common.

The reason why I pointed out this thing about home administration is there is a general feeling in the community that palivizumab is relatively safe to administer at home. We have not really seen anything that is a strong hypersensitivity signal.

We went back and talked to our safety people and they didn't say that we saw any new signals or anything that is not described in the label. Going back to the original study, the overall frequency of higher-grade hypersensitivities was at 0.4 percent which is comparable to what we are seeing in this current study. That is palivizumab.

DR. HENDRIX: Dr. Roland.

DR. ROLAND: My question is about study design and how you thought, or think about, the noninferiority margin.

My understanding is that it is powered to accept a 50 percent loss of efficacy compared to the product that is currently on the market. I am just wondering if you consider the loss of efficacy relative to a product that currently has a lot of side effects or is difficult to administer.

How do you weigh that?

DR. SHAPIRO: This is part of the decision we are putting onto you, basically, are asking you about. This is what we see in regard to hypersensitivity. This is what we saw in regard to efficacy and noninferiority. We showed you how the margin was maintained, how it was calculated and how, in the primary analysis, motavizumab did meet noninferiority.

But I think this is the thing. These are decisions that it is not easy to quantify.

DR. ROLAND: That is actually not my question, though.

DR. SHAPIRO: Sorry.

DR. ROLAND: I am just trying to understand, when you initially met with the sponsor about the study design, and they presented to you that this was their plan and the

noninferiority margin that they were planning to look at, what considerations did you have at that time? Did that seem fine? Or how do you think about an acceptable noninferiority margin.

DR. SHAPIRO: Well, one thing, as we mentioned, is that the study was started before we had the full end-of-phase-2 study and a lot of comments were passed forward at that time in that May meeting. It had been started in the RSV season preceding. A lot of things got started--before a full discussion was done, the study went underway.

So I think probably in hindsight it is always best to have your end of phase 2 and then start phase 3 because then things that you learn from your phase 1 and phase 2 can be incorporated into your design.

DR. SOON: Greg Soon, statistical team leader from FDA. I want to add that we took this over after the margin was already determined. But just as a general consideration for the margin it is based on palivizumab versus placebo on effect size.

The reason we are taking 50 percent discounting is because we are researching the new population versus the old population. We don't know at that time so it is really

typical to say we just do something to be a little more conservative. It turns out somewhat different, as you heard early, both in terms of attack rates and also in terms of composition of the population.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: I guess this is a question for the FDA and the sponsor and just clarifications. I seems that the primary endpoint was based on RSV respiratory hospitalizations and whether or not to hospitalize was more subjective per site as opposed to objective with specific criteria.

I have not seen any data on whether or not these subjects were co-infected with other viruses such as adenovirus, rhinovirus, human metapneumavirus virus. I know from a practical point of view, at some centers, once the RSV is positive, further testing does not occur unless it is specifically requested.

I was wondering if any thought was given to that.

DR. SHAPIRO: I can tell you, looking at--I came into this on the later side, but I can say, when we went back to the data, there was a period of time that an assay called the Hexaplex was done would enable you to identify

other respiratory viruses other than RSV.

But that was used for a short period of time for about 600 patients. And then the sponsor switched to a real-time RT-PCR method which is specifically targeting RSV. So we don't have information for most of the specimens of whether there was a co-infection or not.

DR. ZUPPA: Just to clarify, I think a co-infection would, just to state the obvious, make children a little bit sicker.

DR. O'REAR: And the switch was because the original assay was not detecting RSV-B.

DR. SHAPIRO: Yes, so that the Hexaplex was not--so they were losing out on RSV-B-positives with the Hexaplex.

DR. ZUPPA: Again, so the definition of chronic lung disease could be anything from supplemental oxygen requirement to tracheostomy and mechanical ventilation. I have not, again, seen any data looking at that subset of patients in both the 110 and the 124 study of patients who had tracheostomies and were mechanically ventilated because I would, again, suppose that an RSV infection in lungs that are that sick would probably warrant further

hospitalization.

DR. BIRNKRANT: I think we can refer that to the applicant.

DR. HENDRIX: I have got Dr. Freeman and then Ellenberg, Graham and Ralston.

DR. FREEMAN: I have a question that is kind of along the same lines as the coinfection but a little bit different. So I think a lot of the presentations have talked about the lack of sensitivity of the EIA test and the other tests. When you think about the PCR tests, they are really sensitive.

So one question--I didn't see this brought up in the reading material either, but I was wondering about--you know, sometimes when a baby comes in with RSV infection, positive RSV PCR, they get better, but the PCR may stay positive for a time after that.

And the baby was just sick. So then let's say they start wheezing again it is a different cold and they get readmitted for wheezing. Did anyone think a little bit about how to distinguish then, is that a true RSV infection at that point with that continuation because I can see that, then, you would kind of build up your hospitalization--I can

see that could maybe confound things a little bit.

DR. BIRNKRANT: I think MedImmune can answer that.

DR. FREEMAN: Okay. And then I had a second question. So the MedImmune people had shown the pictures of the actual hospitalizations showing the decrease and maybe the days of ICU, the days on mechanical ventilation. Did your group look at that as well and in terms of statistically significant of that as well and was that--were there regional differences there?

I mean, that may be one place where you might be able to tease that out.

DR. TAUBER: Well, in 110, we did look at respiratory hospitalizations overall in terms of severity. They were, apparently, less in the motavizumab arm compared to the palivizumab in 110 which we found reassuring.

DR. HENDRIX: Does the sponsor want to answer the question? Could you restate the question again just so it is clear to them?

DR. FREEMAN: The PCR question?

DR. HENDRIX: Yes, please.

DR. FREEMAN: My question is about kind of the length of the PCR testing positive, because you can have

some shedding, some PCR positivity, that may last longer than you expect with the EIA.

So my question was kind of like how do you tease out--if someone, then, is wheezing after their RSV infection--you know, these are kids with bad lungs anyway. So then they wheeze more and how do you kind of tease out is this a second hospitalization related to RSV or is this related to wheezing or is there related to a second virus but they are still RSV positive, that whole kind of issue.

DR. CILLA: We will ask Dr. Losonsky to address that.

DR. LOSONSKY: I think that is a great question and it is something that there is not a lot of guidance out there in the literature on. So I will try to address it by telling you we did have a protocol-specified window of two days, plus or minus two days, from the illness to collect the sample.

Slide on.

[Slide.]

So, if you look at those samples that met our analytical window for admission for hospitalizations at the top, you can see that the majority of those were collected

within the defined time.

To your point, we did have a broadened time period for collection and that was because of the data on PCR that it is highly sensitive. But we had a cutoff of 11 days based on our data from our treatment trial, CP106, which suggested that children acutely hospitalized with RSV would persist with a positive PCR and that timing seemed to be appropriate for that acute event.

So I think I will leave it at that and Dr. Suzich may want to comment some more in our research division on PCR detection.

DR. SUZICH: As has been discussed, we were very concerned about that. In our treatment trial, CP106, we saw that subjects were positive by PCR for about seven days after drug was administered, after they had been hospitalization for RSV.

But then we lost the ability to detect signal at 30 days. But we don't know in between them.

I can tell you that we did collect specimens from healthy people during the RSV season just to ensure that we weren't, by PCR, picking up background noise. And we didn't see just noise in nasal specimens collected from people who

were healthy but in the community around the time that RSV was in circulation.

DR. FREEMAN: That is helpful. Do you have any idea, like, how many patients were actually readmitted, how many hospitalizations were actually the same patient being rehospitalized in that data in terms of RSV?

DR. CILLA: It is my understanding that there were only two subjects that were rehospitalized in all of our trials.

DR. FREEMAN: Oh; well, that makes it--

DR. CILLA: Each of them were only counted once.

DR. FREEMAN: Okay.

DR. LOSONSKY: Readmissions do happen. I think as Dr. Ramilo said in his presentation that readmissions or reinfections with RSV do happen.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: On Slide 11, you showed the construction of the margin and you said it was based on a meta-analysis of two prior placebo-controlled trials of the active comparator. So one important thing in setting a margin, as you know, is whether there is a constancy of effect across studies.

Of course, two studies is the absolute minimum you can have to think about constancy. You would really like to have more than two. Can you tell me what the actual effects were in the two studies that led to the estimate of 2.028?

DR. TAUBER: There was only one study, one large study, during the approval of palivizumab and that was the one they based this on. We did not--it was a 1,500-patient study, 2-to-1 randomization, between palivizumab and placebo.

DR. ELLENBERG: But it says meta-analysis of two studies on the slide.

DR. TAUBER: I guess perhaps--048 wasn't

DR. ELLENBERG: So you can't assess constancy. You only have a single estimate. This 2.028 was from a single study and you have no idea that, if there was another study, it might have been something very different.

DR. SOON: The comparison was one study, one study only.

DR. TAUBER: At the time that the 1.265 was determined, Study 124 hadn't yet even come into being. So that was the only study. The 018 was the only study that was considered.

DR. ELLENBERG: Okay. So this slide is not correct, that this was based on--I just want to make sure I understand because the slide says meta-analysis of two studies but you are telling me it was really only one study. That is an error. Okay.

The next question--this is very simple and straightforward. On Slide 16, if you can show Slide 16 again, I wanted to make sure I understood exactly, in this process, when randomization occurred and when treatment started.

DR. SHAPIRO: You are talking about 16; right?

DR. ELLENBERG: Yes.

DR. SHAPIRO: Basically, this is a prophylaxis study so the randomization, of course, occurs before the whole algorithm.

DR. ELLENBERG: Oh, right; of course. Okay. Thanks.

DR. HENDRIX: Dr. Graham.

DR. GRAHAM: I just wondered if the FDA could give us a sense of a context for the hypersensitivity that occurs with motavizumab and whether it is higher than other antibodies that are administered or higher than other drugs

that are given to 100,000 or so subjects a year or higher than other drugs given to this kind of population.

DR. SHAPIRO: I can give you some numbers. Looking at vaccines, which are active immunizations as compared to passive which is palivizumab and motavizumab. The frequency is quite low. It is about 0.65 per million doses of vaccine given. So definitely we are talking about 56 per 10,000. So that is quite a bit larger.

If you are getting something comparable you would be having hypersensitivity more on the lines of something very immunogenic like penicillins. You can sometime see things at about 1 to 5,000.

You asked me for two examples and one is penicillin and the other one, of course, is vaccines which, in general, have a fairly low anaphylaxis rate.

DR. HENDRIX: Dr. Ralston.

DR. RALSTON: So this is back to how the noninferiority bound is calculated. Again, it was based on assumptions that this is the same population as in the original palivizumab versus placebo study. And it turns out that that is not the case; right--that the current mota versus pali, there was a significantly different number of

patients with chronic lung disease which is clearly going to impact the risk of hospitalization.

I am curious how that should impact on noninferiority, or if it--

DR. SHAPIRO: I am going to refer it back to the statisticians but one of the problems is when you have two different population and you are calculating noninferiority based on history, you have to be concerned about, you know, historical because, back in the original 018 trial, the amount of CLD to non--the amount of CLD was much higher than it is in this study.

DR. RALSTON: Okay. I am curious with the statistician's extrapolation, about what that would do to the noninferiority bound.

DR. MURRAY: Can I just comment on the noninferiority slide because I made it. It is true. There were two studies. It was recalculated at some point probably after the end-of-phase-2 meeting. But there were two studies, one that was 1500 in the lung disease but then there was the Cardiac study.

Both of them about had a 50 percent reduction in RSV hospitalizations with pali. So there are two placebo-

controlled pali studies which show roughly about a 50 percent reduction in the lower bound of a 50 percent reduction in risk, so about twice as many RSV hospitalizations on placebo compared to pali.

DR. RALSTON: How big was the Cardiac study?

DR. MURRAY: It was 1200.

DR. HENDRIX: Jeff, can you state your name and affiliation.

DR. MURRAY: Jeff Murray, Deputy for Antivirals.

DR. HENDRIX: Thank you.

DR. NEI: Do you still want me to answer? I am the statistician.

So, with CP110--that is the primary study--so that does not have the cardiac population. So I think CP018 is appropriate to use to define the margin. So I, indeed, checked the population difference.

We recently published a paper that particularly talks about that. So we, indeed, used the logistic-regression model and investigated which factor interacted with treatment. If they interact, that implies potential heterogeneity, we included inside and calibrated the effect. And we confirmed the site of 1.265 is appropriate.

The reason we didn't use the other study, CP048, is that it is a different study population, different than CP110. Originally, we didn't include CP124 for the noninferiority investigation.

DR. RALSTON: So for the specific question about the difference in the populations,here is my assumption. In the initial pali versus placebo study, the hospitalization was higher.

DR. SHAPIRO: Correct.

DR. RALSTON: Therefore, it is going to be easier to detect a difference in the hospitalization rate.

DR. SHAPIRO: Correct.

DR. RALSTON: In this study, this included a patient population that should have a lower hospitalization rate--i.e., fewer patients with chronic lung disease and, therefore, the hospitalization rate may be even lower and, therefore, more difficult to detect in the noninferiority bound, maybe.

DR. SHAPIRO: I think you are right on the mark with back in the 108 study which occurred in the mid-to-late '90s. There was a higher attack rate. There was a higher proportion of those with CLD. There was a higher proportion

of those less than 32 weeks. Currently, the current study has less CLD.

The other thing is one thing I can say from general consensus--I have spoken the physicians, neonatologists--that we are hospitalizing less kids that we used to for RSV. So that all impacts because you have an attack rate. But you also have a decreased--if you are less likely to hospitalize a patient because of current practices, your hospitalization rate is lower and, therefore, you are having a much smaller rate to calculate to compare differences to.

DR. NEI: Sorry. I forgot to mention one thing. CP018 is just the population U.S., British and Canada, three countries. In CP110, it is an international study. So, when we calculate the site, the noninferiority margin, we are still taking no geographic difference. But, that assumption could be wrong. But we don't know. There is no idea how to assess that.

DR. HENDRIX: Dr. Atkinson.

DR. ATKINSON: I wanted to ask a question about Slide 39 again. I hate to keep beating this horse about this timing of the hypersensitivity reactions, but if you

look at that slide, there is not really any pattern that particularly jumps out. But aren't we culling out the people that are having reactions?

You said that there is a tendency to have reactions, repeat reactions, and we know that there is an association with antibody.

In Slide 40, the timing of the more severe reactions, wasn't that towards the end of the study?

DR. SHAPIRO: There were quite a few that were--I counted up, as I gave you, about nine that occurred with the fifth dose. That patient that we are referring to in CP118, even though it was the third dose, it was on the second season so that could have been the eighth dose.

DR. ATKINSON: People that had a reaction on the last dose, were they discontinued from the study or were they still--

DR. SHAPIRO: Well, they were followed for safety. Why I mentioned that is you can't say that you are discontinuing them. They have finished their dosing so many of those patients, if they were to get a sixth dose--let's say they were in Florida which has a longer season where you may get six doses, they may have discontinued them there and

not given the sixth dose.

That is why I mentioned the caveat about the fifth dose. You don't know because they are already at the end whether the physician would have given them another dose or discontinued them because they had already come to end of their dosing regimen.

DR. ATKINSON: Was there a larger number of discontinuations early in the study like in the second and third dose? I thought I remembered reading that but I couldn't find it. Because it is a big drop. I noticed there is a big drop after the second dose.

DR. SHAPIRO: No, no. The thing is that what you are doing here is you are seeing that, if you are looking for motavizumab, you would have to say about half is third dose and later. Let me just pull it here, because I have the actual dose numbers here.

Looking at the grade 3s that led to discontinuations, there were many that were dose 4. This is CP110. Dose 3. We had one in dose 2, dose 4 and dose 4. So many of them were on the late side. This is just looking at CP110 motavizumab.

DR. HENDRIX: Dr. Walden. I'm sorry; Ms. Walden.

MS. WALDEN: I have just a medical question here. I am here as a patient advisor. Almost every package insert that you read or warnings signs on medications, they always have something related to skin irritation, perhaps. And, also, I remember my 24-week-old premature baby that I brought home after infection after infection and multiple reactions to drugs and terrible skin integrity at birth and thereafter, even after I brought her home, I wonder if you have a child like that that already has decreased or compromised skin integrity, if you have a reaction to a drug, would it increase, then, the level of skin interaction from a drug reaction.

Is that clear?

DR. SHAPIRO: I am not sure I can give you an analogous example but it is not the same. We do know that certain patients that have chronics such as the spina bifida, they get multiple exposures to latex and they have a higher degree of latex sensitivity. I am just trying to give you an example where people have looked at patients who have a compromised system.

That is not a direct analogy to this but am just saying that patients that do have underlying conditions

sometimes do have a higher degree of hypersensitivity reactions to things that they are exposed to.

MS. WALDEN: I was just asking for my own perspective here, just medically, is that possible to have--in a normal child, you may have a minimal skin reaction to a drug. If you have a child who has had prolonged hospitalization, repeat infections and that kind of thing, if diminished or compromised skin integrity would then be intensified if you have a drug reaction. It is just a medical question.

DR. SHAPIRO: I think the problem is whenever you have a compromised host or a host under underlying conditions, they do experience a lot from the medical community, whether that plays a role or whether there is an inherent tendency to allergy because you have inherited it, basically a family history. They all play in.

Patients that are in the medical system longer, you do sometimes see more reactions to drugs because they get multiple exposures. But I am not sure I can directly--this is all observational. This is not a true scientific type answer.

DR. BIRNKRANT: Maybe it would help of MedImmune

could answer whether or not serious skin disorders at baseline were an exclusion criteria.

DR. CILLA: I was also going to offer--with the chair's permission, we do have a pediatric immunologist-allergist who specializes in dermatology disorders that potentially could at least provide some answer to the initial question.

DR. HENDRIX: Sure. Why don't you answer both of those, then.

DR. HENDRIX: Dr. Boguniewicz.

DR. BOGUNIEWICZ: As a clinician, I can certainly attempt to answer a parent coming with those kind of concerns. And I would say, as our colleague from the FDA mentioned, that this is complex. While we continue to study this, we know that so many of those adverse reactions, in fact, don't have any defined immunologic underpinnings, that we are just starting to scratch the surface of trying to understand how our unique genetic makeups allow us to be more predisposed to various adverse reactions.

So there are many things acting on that skin, some of then affecting the immune system but certainly some of them definitely not in the immunologic arena that can result

in a patient's presenting and, depending on what else is going on, as you correctly point out, various infectious agents drive the immune system to react.

Here the focus is on respiratory syncytial virus but, as others in the group have pointed out, these patients can have multiple infections. So I think that, stepping back here, looking at the whole picture, we are dealing with a population of sick patients who certainly have the potential to have adverse reactions for a variety of reasons.

Some of them don't really--aren't easily classified.

DR. CILLA: And then to directly answer the question about whether there were any exclusion criteria for the protocols directly related to skin disorders, there were none and we did print out a copy of our inclusion-exclusion criteria and could share that with the committee if they so chose.

DR. HENDRIX: Thank you. We would be happy to receive those.

It is 1204 hours. We are going to break for lunch. After lunch, we will have the Open Public Hearing

session if there is someone that is signed up.

After that, we are going to finish the clarifying questions both for the FDA and for the sponsor. I have, for FDA, Dr. Maldonado, Clay, Freeman and Strader. For the sponsor, I have Dr. Clay, Graham, Freeman, Zuppa and Havens. You can certainly add your name to this list if you think of something in the meantime.

But I will remind you that the members will not be discussing any of this during the lunch amongst ourselves or with any member of the audience.

In terms of the lunch, let me just remind you to please take any personal belongings you may want with you at this time. The ballroom will be secured by the FDA staff during the lunch break.

As I recall, commission core are the uniformed service members who do not carry weapons, but the room will be secured by the FDA staff. Again, the reminder to the panel members not to discuss the topic during lunch.

I thank you. See you back at 1 o'clock.

A F T E R N O O N P R O C E E D I N G S

[1:02 p.m.]

DR. HENDRIX: Welcome everybody back from lunch.

Open Public Hearing

DR. HENDRIX: There will not be an Open Public Hearing. No one had submitted ahead of time and no one has signed up for today, so we will, at this point, continue with the clarification questions for FDA.

Clarifying Questions for FDA and Applicant

(Continued)

DR. HENDRIX: Let me clarify what we are going to do. We will finish the clarification questions for the sponsor and then we will have an open discussion among the Committee members for things other than clarification. So we have got an hour to do the things that I just mentioned.

And then, at 2 o'clock, Dr. Birnkrant will give us the charge for the three specific questions. We will do those in turn as we go through. So there will be responses to that and more discussion as well, but, if there are specific things in the discussion after clarifications, we

can talk amongst ourselves here in the open session to sort those things out.

Let me go ahead and start. So, for the FDA, then, for the clarification questions, I have Dr. Maldonado and then I also have Drs. Clay, Freeman and Strader. And then we will get to the sponsor clarifications unless there are still others for the FDA.

So, Dr. Moldonado, you can start.

DR. MALDONADO: Thank you. I just noticed we got some inclusion-exclusion criteria here. But my question, and I guess I am just trying to get Slide 11 on the BLA handout and Slide 7 on the RSV Infections Intro kind of straight in my head in terms of what we are trying to compare here.

I actually didn't have time. I was going to try go back and look at the original paper to see how the two studies were different. But, obviously, it is a different population. My question really has to do with I think the statistician--I am sorry, I forgot his name--but he alluded to the fact that he did so some logistic-regression analysis

looking at trying to kind of stratify--or at least make those comparator groups more even.

I would like to get a little bit more information about what the variables were because I think that is critical. I mean, we are talking about a 12-year difference in enrollment, or maybe less, ten or so. But, still, it isa fairly substantial difference in population and I know at our center, and I am sure others, these children--we are hospitalizing less children but the children we are hospitalizing are sicker. So I don't know how statistically you would adjust for that.

The second question is probably simpler. I am not thinking clearly, I guess, but when I look at the confidence interval for this, and it is just for the first study--it is not for the Cardiac study from what I understand--the confidence limits for placebo versus pali is 1.529 and 2.717.

You are trying to get a better effect than that compared to placebo; is that correct? And, if you are, then--I mean, this is going to come up in our discussion

because we are going to be in between that 50 percent and the actual effect that the drug came up with. So it becomes very critical to understand how--and I know you don't have--you did this before the studies were completed but, in fact, this is going to be our question. So how you came up with that number is going to be important.

DR. SHAPIRO: I will start, but I will ask one of our staff people also to come up. Basically, the point was that, when you calculate a noninferiority margin, you basically take historical--because we are trying to assume placebo.

DR. MALDONADO: Right.

DR. SHAPIRO: You have a confidence interval around the older study and you have it from 1.529 to 2.717. What you do, because--we are talking about right now the M2 basically, trying to do that.

DR. MALDONADO: Right.

DR. SHAPIRO: We get some leeway because there are differences over time. And you are asking yourself what is the minimal effect you want to have over placebo to feel

that your drug is now comparable to your control which would be mota comparable to palivizumab.

So, when the statisticians met and discussed--when this was discussed with the applicant, they came up based on taking a lot of factors into account to come up with a thing where we felt we had to preserve at least half of that difference there and still call it noninferior because the problem is their ability and such and things are different over time.

You try to do your best. You try to set what that M2, what the lower bounds will be that you will accept. So I think, at that time, based on all the information, they set that lower bound. Like I say, I wasn't physically there at that particular meeting but I do know that this is frequently done when people calculate a noninferiority margin is that they have to make a given of what are they going to accept and still think there is--it is still an inferred. It is not a direct but an inferred difference with placebo.

DR. MALDONADO: And then to answer the other

question about what factors were taking into consideration in equalizing those two studies.

DR. MURRAY: I think, after the fact, the sponsor did a sensitivity analysis on the noninferiority margin to look at the differences in the population enrolled because I think 110 had maybe a lower proportion of CLD than the palivizumab studies. Actually, the treatment effect for palivizumab versus placebo was better in the non-CLD patients.

So, the margin, if you consider that factor into it, could have been a little bit larger because 110 actually enrolled more patients where, in the previous studies, pali was even greater, had a greater that effect on placebo. That was one of the sensitivity analyses done in the noninferiority margin.

This is all a matter of judgment and that margin can move to the right or to the left depending on a lot of factors and assumptions. This is typically done, what we are doing for noninferiority margins, a 95 percent confidence bound around the treatment effect and taking half

to ensure that at least having that can be better than placebo.

Jeff Murray, Deputy.

DR. SOON: Greg Soon, Biostatistics Leader from FDA. I would like to have the reviewer Lei Nei to provide some numbers to show the differences.

DR. NEI: Basically, the idea is what the chair has just said for several different population differences in chronic-lung-disease status. In the original population, it was 50:50. In the new population, it is 22 percent:78 percent because the treatment effect in the disease status, they are different. So we need to cut categories of the treatment effect.

But not only this is a factor. We will need to investigate many others with regard to heterogeneity. We find out some slight difference in gender, also find out differences in asthma history.

So we find three factors could interact with the treatment effect. We include all of them, including the chronic lung disease, asthma history and gender, put them

together to calibrate the effect, and we found out 1.265 is appropriate. That is what we do.

DR. MALDONADO: So you didn't find the gestational age was an interactive factor.

DR. NEI: That is also originally a question from the medical officers, Bill and Alan. I checked carefully gestational age. Individually, no. It could be confounding with the others--for example, chronic lung disease. We checked that, too.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: So, just to clarify because I am not familiar with the concept of adjusting the margin based on observed differences in populations. I had thought that what you meant was that the margin, itself, was constructed on the basis of the prior studies. And now I think I am still hearing some saying one, some saying two.

But the 50 percent, the M2, is where your judgment comes in in terms of how much you can preserve and all of these other factors sort of go into that. That M2 might change if you were more worried about that the population

might not be the same.

But, this 1.265, was that actually--did the differences in the populations actually go into the calculation of that or did these differences affect your choice of the 50 percent as the M2?

DR. NEI: So we--after adjusting and calibrating the effect, we constructed a 95 percent confidence interval. The lower bound is 1.56, something like this. Then you take the square root, and you get 1.265.

DR. ELLENBERG: No. I don't want the details of the mathematics. I am not sure what you mean when you say "calibrate." I want to know--

DR. SOON: Let me put it this way. The original margin was based on--it was done before the trial was initiated. So that was based on the assumptions. Basically, the 50 percent was a pre-emptive strike to say, you know, maybe there was different information and we don't know what is going to happen. So, let's have some conservativeness in stating the margin.

However, when see the actual trial, we have to

make sure that we still have reasonable--we don't too much diversion from what we would have expected in the design stage. If some of the results are different, you don't see any events in the new trial, that may rest out.

But even the 50 percent discount, that was where the additional analysis is coming from, and we are trying, with the other covariates, to see how the population compares between the new study and the old study.

If we adjust for certain key covariates, we are going to change the margin post--knowing the real data.

DR. ELLENBERG: So did you do that is or is 1.265 directly calculated from the estimate from the prior study and then the 95:95 method?

DR. SOON: Yes.

DR. ELLENBERG: Yes, it was?

DR. SOON: Yes. It was based only on the original study, CP018, not adjusting for any covariates.

DR. ELLENBERG: Not adjusting for any covariates. So this 1.265 is not calculated based on any covariates.

DR. SOON: It is not based on any measure in the

new study. There is no attempt to measure because that we determined before the trial was started.

DR. ELLENBERG: Right. Okay.

DR. SOON: So we did attempt to see if that margin still holds knowing what we know of the trial results.

DR. ELLENBERG: All right. But that is the margin that you are using, the one that was originally calculated at the beginning. That is the margin that we are looking at.

DR. SOON: As Jeff also mentioned earlier, one of the difficulties is we cannot account for all the factors. I mean, there are so many different factors--for example, region. The trials were done in different places. How do we account for that difference? We had to make some assumptions saying probably that is not an effect we can ignore.

DR. ELLENBERG: So the answer is all these other factors are things that you are looking at and are helping to interpret the results.

DR. SOON: Correct.

DR. ELLENBERG: But they do not contribute to the construction of this margin. This margin is simply based on the results of the prior studies of Synagis.

DR. SOON: Yes.

DR. ELLENBERG: Thank you.

DR. SOON: The 1.265 is based on the original data.

DR. HENDRIX: Dr. Clay, Freeman, Strader and Veltri.

DR. CLAY: I am not going to ask a math question, I promise. My question relates to the CP117 the FDA recommended or directed the sponsor to conduct. So I have to assume, if they encouraged them to do that study--no? Is that incorrect?

DR. SHAPIRO: It is not that we encouraged them to do the study. This was a population being studied by--the principal investigators actually were at Hopkins--who looked at this population and characterized them. There is a publication in Pediatrics, and there are other publications, indicating that this is a high-risk group.

This 117, I wasn't there at the time, but it was a study that was exploratory in its original origin to see whether an intervention such as motavizumab could make a difference in this population.

DR. CLAY: So the fact that there is not a third arm in this study that would have allowed for a comparison between placebo and mota--

DR. SHAPIRO: And palivizumab.

DR. CLAY: Yes. That wasn't a recommendation to the FDA to add that third arm so we could actually see--in this population which we really didn't know what the benefit of this drug would be, we would be able to compare those two active.

DR. SHAPIRO: I think the thing was--originally, what happened was based on some of the data that we got from 110. We asked them to include 117. 117's original design was not as much to support the efficacy of motavizumab but more of an exploratory in this particular population. As we we had concerns, we then encouraged the sponsor to bring in that data as part of their package.

DR. CLAY: Okay.

DR. HENDRIX: Dr. Freeman.

DR. FREEMAN: I am not sure if my question is better for the sponsor, but I will just ask it.

I just have some questions about the antibodies, the anti-drug antibodies. I was wondering if they have been looked at for any cross-reactivity between the two since the two drugs are fairly similar minus several--I guess, what was that, 13-or-something amino acids--only because if these ADAs are then going to account for some of this hypersensitivity and then, in this vulnerable population, you switch to a different drug, is there going to be any cross-reactivity.

So that was kind of my question, like, if people are looking at this.

DR. SHAPIRO: I can refer you to the applicant but there was a study in which they did dose one versus the other and looked at them.

DR. FREEMAN: Oh; okay.

DR. SHAPIRO: It would be 127. So they can answer

more questions about what they found.

DR. FREEMAN: Right. That would be great.

DR. HENDRIX: Sponsor, do you want to answer that?

DR. CILLA: Would you like to answer the cross-reactivity question first?

DR. FREEMAN: Yes.

DR. CILLA: And then the clinical question?

DR. FREEMAN: Yes; and then the clinical question.

DR. CILLA: Perfect. Dr. Robbie will address the cross-reactivity question.

DR. ROBBIE: Since the difference between palivizumab and motavizumab is only 13 amino acids, it is completely conceivable that there might be cross-reactivity. For the consequences, I think I will ask the clinicians.

DR. FREEMAN: Well, was it looked at in vitro, cross-reactivity?

DR. ROBBIE: There are two assay formats. I need to cross-check and get back to you because they used a new format only at the latter stages, not in the study where both palivizumab and motavizumab were used. So let me check

and get back to you.

DR. FREEMAN: Okay. That would be great.

DR. CILLA: And then for the second question regarding CP127, the study in which both agents were administered, are you interested just in the safety profile and whether there are differences or--

DR. FREEMAN: Yes. I am interested in the safety.

DR. CILLA: Okay. Thank you.

DR. FREEMAN: And if there other interesting things about it.

DR. GRIFFIN: CP127 was a study that we did looking at sequential dosing of palivizumab and motavizumab given in the same season. So we had two doses of one antibody and then switched to the other for the remaining three doses.

We also had a control arm of five doses of motavizumab. So we had active drug for all three arms of the study. It was a small study.

Slide up.

[Slide.]

This is the overall AE summary. You can see that there were just over 80 to 90 subjects in each arm. This is the motavizumab-palivizumab arm, palivizumab-motavizumab, and motavizumab only.

When we looked at it--it was interesting. We did see that it seemed like there were more Level 3s than SAEs in this arm. So it made us look into it further.

And if I can have S37. Slide up.

[Slide.]

This shows that, when we divided it--this is before the switch and then after the switch--it seemed like there was something different about this group in the beginning because there were more SAEs in the beginning here which, in the mota-pali group--and they had only gotten two doses of mota here, so more here than in the mota-alone group--it was hard to draw definite conclusions from this study since it was a small study.

When we investigated it, we didn't find any reason for this group to be any different than the other two groups.

DR. FREEMAN: Were there any of the hypersensitivity reactions in any of the patients that had switched from the mota to the pali?

DR. GRIFFIN: We did have an erythema multiforme but that was after two doses of motavizumab and before the switch.

DR. FREEMAN: And then no problems after the switch?

DR. GRIFFIN: In terms of additional hypersensitivity?

DR. FREEMAN: Yes.

DR. GRIFFIN: No.

DR. FREEMAN: No?

DR. GRIFFIN: No.

DR. FREEMAN: All right. Thank you.

DR. SHAPIRO: I would like to make an additional comment, if I may, about this. In Study 118, which was the second season of those patients who had been dosed in 104 in the phase 1 study, we had 12 patients who developed anti-palivizumab antibodies.

DR. FREEMAN: Okay. That is helpful, too.

DR. HENDRIX: Dr. Shrader.

DR. SHRADER: This might be better for the sponsor, too. Are both of these drugs fully humanized or are there murine components in either one of them?

DR. CILLA: I would like to invite Dr. Suzich to answer that question.

DR. SUZICH: Motavizumab is more fully human than palivizumab. There were two murine residues in the framework of palivizumab that were replaced with human residues in motavizumab. The CDRs, though, contain murine residues.

DR. SHRADER: Then a question for the FDA. The three patients that you thought may have anaphylactic responses, did they have ADAs?

DR. SHAPIRO: The one patient that was referred to, the one in 118, they did not find any ADAs in. I don't have the data on the other two.

DR. ROBBIE: We looked into three patients. CP118, the second season dosing, that was not ADA-positive.

CP124 was ADA-negative and CP117 as well. All three patients were ADA-negative. And the concentrations.

DR. HENDRIX: Dr. Veltri.

DR. VELTRI: I thought I had this clear, but maybe I got a little confused from Dr. Ellenberg's question again. Just to be sure, I want to get the process straight. The margin was set before any data was looked at and that was for both the trial 110 as well as the pooled analysis, 110 and 124.

All of these other things that are being looked at here regarding the margin are post hoc. I just to make sure that the margin was set.

DR. SHAPIRO: As was discussed, the margin was discussed beforehand, more--

DR. VELTRI: And no changes occurred before unblinding, the data-analysis plan?

DR. SHAPIRO: No. That is correct.

DR. VELTRI: Okay. That is good. The question I have relates, again, to this question of the local RSV positivity and what relevance that may have versus the PCR

and whether there is any bias there.

My understanding, in both the FDA and the sponsor presentations, was that approximately 11 percent, a subset, actually had local measurements.

DR. TAUBER: 11 percent of all respiratory patients.

DR. VELTRI: Right. And then, when you look at that 11 percent, it didn't really matter whether they were positive or negative. Either positive or negative, there were 50 percent, approximately, admissions, regardless of that in both arms. 50 percent of those patients, whether they be positive or whether they be negative in that analyzed subset were admitted.

DR. SHAPIRO: That's correct; about half of them, a little more than half of them had local measurements.

DR. VELTRI: So the question I had, since we are trying to understand what that means, has anyone looked at actually the demographics within the study groups, not between the study groups, of, perhaps, what their clinical risks were and their outcomes?

In other words, if it didn't matter whether you were positive and negative and they were all hospitalized, were there any differences in the demographics such that, knowing whether they were positive or negative, they still had the clinical acumen--that the investigators admitted them because they were of equal risk regardless of what the assay showed. Are you following me?

DR. SHAPIRO: I am following you sort of. But, with equal risk, a lot of decisions--just speaking from my past days where I was sitting in and making decisions on admission, a lot of times it is your clinical presentation of whether you think the patient is going to be able to be maintained at home or not.

That is the primary decision-point in a lot of patients when you admit them for RSV. You don't think they can take down fluids. You don't think they are going to be able to maintain sufficient oxygenation. They are too hard to maintain at home. These are all things that you take into account.

But there are, as I mentioned in my presentation,

some patients who are on the borderline who you sit on in the E.R. and you are just saying, do I bring them in, do I send them out? A lot of times, there are other factors that come in.

Sometimes what we are hypothesizing is that, in those situations when a local test is obtained, that it can skew your results if you then get a local test that is RSV-positive. You say, oh; they are RSV-positive. They are likely to have a more severe course. I am going to bring them in.

DR. VELTRI: But if an equal proportion were admitted, was there length of stay, the need for mechanical assist, other things within those--not between groups but within groups, even though the numbers are smaller to try, again, to suggest that, indeed, this was really clinical acumen which really decided whether they got admitted or not, and there was really no difference whether they were assay-positive or negative.

DR. CILLA: The sponsor would offer--we have a slide that may directly answer some of your questions. With

the chair's permission.

DR. HENDRIX: You are permitted.

DR. LOSONSKY: The slide that I thought might be helpful is the question about the impact of local negative and positive tests in terms of the clinical reasons for admission.

As you know, the second part of the discussion was talking about severity of hospitalization. Actually, our ad hoc analysis suggested overall looking at all children admitted. There appeared to be more severe disease in the palivizumab children who were admitted for RSV.

But, to answer the first question, slide on.

[Slide.]

So this is a little complicated but it is the primary clinical reason for hospital admission on the left, the negative local test results and positive local test results by treatment. Remember, these are kids admitted so we are looking retrospectively at the local tests that we collected during the CRL process.

You can see that the primary reasons for

admission, regardless of positive or negative local tests, were really for acute respiratory care here. Those are quite similar between groups and the rest, as Dr. Shapiro mentioned, were feeling, fluid management evaluation other then respiratory.

These kids, because they are so young, some of the patients may be admitted for a fever workup for sepsis or other types of illnesses associated with their respiratory finding and really a very small number of negative unclear or social reasons for admission.

And these are all respiratory hospitalizations.

DR. TAUBER: May I just make a small comment in reply. It is a little difficult to--we are not saying that the local testing prevented admissions, those that needed to be admitted. It is in those that didn't get admitted that the problem lies.

If you look at palivizumab, the numbers are higher for positives than they are for the motavizumab. So we can't say that having a positive local test did not inform the provider that this patient had RSV.

DR. HENDRIX: We are going to move on. Dr. Hagedorn.

DR. HAGEDORN: Yes. I have a question for the sponsor related to the monoclonals or biologicals. This has to do with the adverse events related to skin events or possible hypersensitivity. So, if the compound or the monoclonal motavizumab is more humanized in structural modeling type studies, is there any suggestion that there might be an epitope that is murine that might be more exposed and antigenic?

The other question I have is regarding the production in the equivalent to compounding of the monoclonal for delivery to patients. Is there any difference in the preparation of the two monoclonals? Are they prepared at the same facility? Is there anything that might be introduced in the purification or the preparation for delivery to patients that could be an issue related to this urticaria that occurred in some patients?

DR. CILLA: It would be helpful to the sponsor if we could delay that question a little bit because the

experts that we need to refer to are not immediately in our bullpen. But we will get the answers to those for you.

DR. HENDRIX: Okay. That is fine. We will come back to that when we get to the sponsor-specific clarifications. Dr. Ellenberg.

DR. ELLENBERG: I wanted to ask about the missing data. In the FDA presentation on Slide 23, it was raised that close to 20 percent of the data on RSV were missing. You hypothesized that the missing data might result in the reduction of the estimate of benefit.

I wanted to ask whether there was any particular pattern to this missing data that might lead you to believe it was more likely that, if the missing data were there, the benefit would have been reduced rather than enhanced and whether there was any attempt to use statistical methods to try and predict what the missing might have been. It is a lot of work in this area, so--

DR. NEI: The reason we brought this into consideration, 19 percent or 18 percent, is because the results are very sensitive for misclassification. Right

now, would you please go back to the slide on the secondary analysis. Oh; the previous one.

[Slide.]

So look at the highlighted version. If, rather than 24, you have 25, the p-value will change to 0.008. From the sponsor's Slide 20, you see there are totally six prespecified secondary endpoints. So you spend already an adjustment if you have the 0.008. It is almost enough to prevent your claim of superiority.

That means, if you have very small changes in the secondary analysis classification, then the result is gone. There is no superiority. That is why we are so worried about this missing data. The results are very fragile.

DR. ELLENBERG: But what I am asking is is there anything about the pattern of missing data that would suggest--I mean, it is also possible that it could be the other way and that the benefit is greater.

DR. NEI: That is right.

DR. ELLENBERG: So is there any reason to think that it is more likely that the benefit is less than that it

is greater? I mean, the data are missing and it is about the same number in each arm. But, in some cases, there might be a pattern of data such that--I know you have gone through these data with the fine-tooth comb, so I am just curious as to whether you think it is more likely that the benefit would be reduced than enhanced.

DR. NEI: Sorry. I didn't take allowance of this. I believe there was no systematic missing data, like you said.

DR. SOON: I would add to this. As you know, we did also an extensive sensitivity analysis regarding to the local testing as well as missing-data issues. Really, we cannot say one way or another.

The two examples you see are from Dr. Shapiro's presentation of range of the possibilities. So we have all the ranges of the possible credible sensitivity analysis. So we cannot pinpoint to one assay and say, this is the way, this is the more variable event or not a variable in the other direction.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: So this is a follow-up to the ADAs when you were asking about--I don't remember who asked--about the three patients that were suspected to have anaphylaxis and there no ADAs.

Were they drawn at a specific time? I don't know if I have missed that--like after each dose or at one point during the study. Were they all drawn--

DR. SHAPIRO: I actually want to address that. That was one of the issues in the complete response letter is that many of the samples in 110 and 117, they were drawn in a period of time where drug was present and would interfere with the detection of anti-drug antibody.

What the applicant did at our request is went back and retested many samples with an enhanced assay called--they abbreviate ECLA--which are drug-tolerant, meaning they could pick up antibodies even in the presence of drug.

So, from our initial overview of the data, we were concerned that they were under-detecting anti-drug antibodies because the drug was present. So you are right on the mark. That was a concern and they did come up with

an assay during the time from receiving our complete response to when they replied with this assay that is more drug-tolerant.

But I think with 118, just to mention, they did go about 120 days out and that is usually far enough out to get an accurate measure.

DR. HENDRIX: So the data was from the enhanced assay? The data that was presented was from the result of the enhanced assay.

DR. SHAPIRO: Correct.

DR. HENDRIX: Is that also true for the results he gave of the negative ADA results for the three anaphylaxis cases that the FDA coded?

DR. SHAPIRO: I think you need to--for 118, we believe that that sample was done 120 days out. That is probably accurate. I am not sure about the other two. Sponsor?

DR. ROBBIE: Yes; you are right. For 118, it is from the old assay. But, as you mention, the sample was collected long after the last dose was administered so the

concentration is below. So it was not interfering with the assay.

For the remaining two subjects, it was for the new assay which is drug-tolerant and robust and sensitive.

DR. ZUPPA: So then, just to clarify, for the other subjects, if a patient withdrew from study because of a hypersensitivity or other reason, the ADA was drawn after that last dose?

DR. CILLA: Would you like us to answer that as well?

DR. HENDRIX: Yes, please.

DR. LOSONSKY: So there were specified study blood draws for ADA and it was--the specified blood draw was--a third would have--and this is 110--a third would have testing post-dose 1, a third post-dose 2, a third post-dose 3 and everyone would have post-dose 4.

So, even if a subject discontinued, they were encouraged to remain in the study for safety evaluation. Almost all subjects did who discontinued and that blood was drawn, then, on study day 120 or post-dose 4 was taken for

virtually every child in the study.

We had a very high study completion rate and that is what that means, that they are followed for the full safety study period of 150 days.

DR. HENDRIX: Dr. Havens. Did you have a question before? Or now?

DR. HAVENS: Oh; this is left over from this morning?

DR. HENDRIX: I saw your hand waving frantically just moments ago. Maybe your chair was about to fall back and hit the ground.

DR. HAVENS: No. I was going to hold my tongue on that one. Thank you very much.

DR. HENDRIX: That's fine.

DR. HAVENS: I am waiting until I get my chance for this morning's questions. Thank you, sir.

DR. HENDRIX: Okay. Dr. Murata.

DR. MURATA: I have two questions. This may be more to the sponsor than the agency-related, but the first question is more of a historical basis. For the licensure

of palivizumab, was the incidence of MA-LRI one of the endpoints that were looked at, either primary or secondary.

The second question is, continuing on the discussion of the ADAs, did the sponsor or with the agency's request look at titers of ADAs, not just simply the presence or the absence of ADA in the patient samples.

DR. CILLA: So the answer to the first question, the simple answer is no, MA-LRI was not used in the original impact trials. And then, for the second sample, I am looking to--so, yes; we did look at titers. If you would like, I believe that we can show some of that information.

DR. MURATA: With the chair's permission.

DR. CILLA: With the chair's permission.

DR. HENDRIX: Please.

DR. CILLA: So Dr. Robbie.

DR. ROBBIE: Yes, we did look at the titers. Slide up, please.

[Slide.]

So, clearly, this is the distribution of the titers in the different patients receiving motavizumab.

This is from CP-110. As you can see, most of the titers for motavizumab are somewhere between 120 and 480. We have, for palivizumab--slide on, please.

[Slide.]

We have slightly lower titers with palivizumab.

DR. MURATA: One extension of this is whether or not the agency or the sponsor has any comments on any potential relationship between the ADA titer and the incidence of adverse events in this particular hypersensitivity.

MR. RYBCZYNSKI: Yes; we have looked at that.

DR. CILLA: With the chair's permission.

DR. HENDRIX: Yes, please.

DR. ROBBIE: Just give me a minute. I need to find out the exact slide. PK102 please. Slide on, please.

[Slide.]

We have looked at the titers of ADA by level 1, 2 and 3. It is actually level 3 skin or SAE. What we see here is that--what we have here is the titer on the Y axis and levels, no skin reaction, level 1, 2 and 3/SAE here.

There is no discernable difference in the levels of skin reactions and titers. There doesn't seem to be any obvious correlation.

Slide down, please.

DR. CILLA: Also, to further answer the initial question about the MA-LRIs being included originally, I think that there was not a general appreciation at the time of the importance of MA-LRI and it was not until there was an effective prophylaxis for hospitalizations that suddenly the MA-LRI severity became more well known. That was why the sponsor included it in subsequent development.

DR. HENDRIX: Dr. Strader, did you have a question for FDA?

DR. STRADER: Yes. I am not sure who this goes to but I am very confused about the interference of MA-LRI with the test, with the assay, itself. You say, in the paper, that if you have motavizumab that it can interfere with the assay's ability to give you a positive test; is that correct?

DR. SHAPIRO: That is correct. What you have to

think about is that the antibody is directed--motavizumab is directed against the F protein.

DR. STRADER: Of the RSV.

DR. SHAPIRO: Of RSV. And let's say you have a local test that also is antibody-based. You can block the detection by having an antibody there.

DR. STRADER: Why does that matter if the RSV is blocked? I assume what we are trying to do, you are trying to block the fusion protein of the RSV so that it cannot bind. So, if I have got a drug that is binding that so that my assay can't detect it, that is a bad thing?

DR. SHAPIRO: No, no. I think the issue is that patient can be RSV-positive and have RSV, but you are not going to be able to detect it because of the presence of the drug.

DR. STRADER: Because it is bound to the drug.

DR. SHAPIRO: But then the question is does the drug--and this is what we are looking at here--when you have the drug bound to the RSV that is being blocked, does it prevent clinical disease. That is the thing. You may have

RSV present and you may be blocking detection, but is that blockage also mitigating the clinical effect that you want.

DR. TAUBER: Let me take a shot at that. As a prevention study, those patients that became infected, obviously, are endpoints. If we are not able to detect that an endpoint has been reached because of interference with the test, then you have a negative result when you should have had a positive.

DR. STRADER: But my understanding is that the whole idea of how we are treating this is to bind that fusion protein so that it cannot--

DR. TAUBER: Right. But--

DR. STRADER: So now we have a drug that does it so well we can't detect it but we are saying that that is interference. I am not sure--how do we know that that is not--

DR. TAUBER: It is a prophylactic regimen, basically.

DR. STRADER: Right.

DR. TAUBER: Therefore, those patients who do have

RSV--let's say that the prophylaxis didn't succeed. They come in for care. They are not being detected as being a prophylaxis failure because the local assay has been blocked by the product.

DR. STRADER: It is still escaping me.

DR. O'REAR: I will take a shot. There are actually several different types of local tests that were used and they varied in terms of the molecular nature. Some of those used an antibody for the N protein. Some of those used the antibody for the F protein. Sometimes, they actually used a combination of the two. And there are other types of assays as well.

But the ones that we are really concerned with are those diagnostic assays that use an antibody that detects the F protein A antigen. That is what motavizumab, that is what palivizumab, targets. So, if you have motavizumab present and binding to all the A epitopes in your sample, there is no place for your diagnostic antibody to bind.

So, in that case, you can't tell that there is any RSV there. So, if you can't see RSV, you are going to

falsely assume that this patient is not infected when, in reality, they are infected.

Does that--

DR. CILLA: With the chair's permission, the sponsor would like to ensure that the advisory committee understands that the RT-PCR assay is unaffected by the presence of motavizumab or palivizumab. That is an important point that we want to make that you understood.

DR. HENDRIX: Thank you for clarifying that.

I am going to move on to Dr. Luque. Again, we have got two left, two more questions for FDA clarification. Then we will move to about half a dozen, at least that we know about, clarifying questions for the sponsor.

DR. LUQUE: I actually think my question has more to do with the sponsor than the FDA.

DR. HENDRIX: Okay. So we will come back to that. Dr. Maldonado, same thing?

DR. MALDONADO: Yes.

DR. HENDRIX: Okay. There being no further questions to clarify for the FDA, we are going to go to Dr.

Clay, a question for the sponsor.

DR. CLAY: In 110 and 117, in some of our background material, it was provided to us that admission decisions versus outpatient treatment, the majority of those were made not by an investigator but by a primary-care physician or an emergency-room physician.

But it was the investigators who were notified of the potential false negatives in patients receiving the drugs. Are you with me so far?

DR. CILLA: Yes.

DR. CLAY: Okay. Good. So my question is when you say the majority of admission decisions were not made by investigators, can you put a number to that for me, please.

DR. LOSONSKY: Well, the simple answer is no, we can't put a number on it. I think the actual people who admitted children would vary depending on when the child appeared, where the child appeared. That is just normal pediatric practice. But we cannot put a number on it.

DR. CLAY: So, in other words, the fact that you had educated the investigators that there could be potential

false negatives, that information was not--you can't prove that that information was then disseminated to the community where the patients were being seen; is that correct?

DR. CILLA: That is absolutely correct other than the fact that one of the commercial test kits has this time of indicated warning in its label.

DR. CLAY: Well, it was for--well, yes. That's right, because it was compared to drug. So they could have been somewhat aware of it.

DR. LOSONSKY: And a further clarification that might help is that what we made aware to investigators was our experience with Binax which is F-protein-binding assay. But we actually found out, through the investigation of the local test false-negative rate, that the false-negative rate actually is a broader effect meaning we are not sure that the effect of motavizumab on upper respiratory virus potentially, interferes with local tests not just by the F protein binding in certain tests that use that, but for an antiviral effect that is more general.

DR. CLAY: So my second question would be with

respect to 117, again. In the other two studies, there were specific statements provided that the individuals were not enrolled in subsequent RSV seasons. But 117 stretched from November '04 to May of '07. So I am curious if people were enrolled in subsequent years during RSV season and, if so, were those individuals--was any sort of subset analysis done on those to look at either safety or efficacy of that?

DR. GRIFFIN: In 117, subjects were enrolled for just one season. So they just got one course of the five doses, monthly doses, of motavizumab or of placebo. They are followed for three years for the long-term outcome of wheezing.

DR. CLAY: So then they wouldn't have qualified to receive it the second season.

DR. GRIFFIN: Right.

DR. HENDRIX: Dr. Graham, you have a question.

DR. GRAHAM: I had two more questions about geography, one about safety and one about efficacy. The first is, were there enough cases to look at the difference in skin reactions in the Southern Hemisphere versus the

Northern Hemisphere? Was there any different distribution of skin--

DR. CILLA: Let me confer with my colleagues for one moment. We do not have that data readily available.

DR. GRAHAM: The second question is about efficacy and it has to do with the Subtype A and B distribution. You had a slide that showed Subtype A and B isolation but that was in people who broke through. The question is did you have data from the community at large on the distribution of Subtype A and B infections and to try to understand what kind of breakthrough responses were happening, because there were other B epidemics on that slide. It looked like the Northeast, for instance, in 2004 and 2005 also had a majority of Subtype B infections.

Were there differences in efficacy in the Northeast, for instance, like there were in the Southern Hemisphere?

DR. GRIFFIN: Actually, what I showed previously was the community--Subtype A and B circulating in the community. Slide up.

[Slide.]

We collected about 4,000 samples from all these regions. We got all the samples we could to try to address the agency's question about circulating subtypes. This is what we found in our investigation. So Northern Hemisphere is here. North America, U.S., subsetted. European Union down here. And Southern Hemisphere here at the bottom.

So, for the year that Southern Hemisphere was in the study, it was close to half and half for A and B from the samples that we got for testing.

Slide off.

DR. GRAHAM: So then the Northeast there has an even more polar distribution of A and B and it is different than the south. So, if you look year-by-year across studies, are there differences in efficacy related to whether it is a B or an A epidemic and do you have information on the breakthrough isolates in terms of whether they were A or B?

DR. GRIFFIN: We have subtypes by study. Slide up.

[Slide.]

So this is 110, 124 and 117. And it is for palivizumab in green, motavizumab in orange, RSV A and B and it is also separated by hospitalization or outpatient MA-LRI for the three studies. As you can see, motavizumab had good activity against both subtypes in all the studies.

DR. GRAHAM: You can only tell about the relationship of the reduction if it is done in comparison to what was in the community. I guess that is what I am trying to ask is relative to the community, what did the distribution of breakthrough isolates look like? Do you understand what I am saying?

DR. GRIFFIN: I do. I don't think we have that breakdown of the data in that way.

Slide off.

DR. HENDRIX: Dr. Freeman.

DR. CILLA: Actually, you had left us with a lot of tasks before the lunch break and we were wondering if you were going to allow us the opportunity to address some of those prior questions.

DR. HENDRIX: We should let you answer those questions.

DR. CILLA: Whenever it is convenient for you.

DR. HENDRIX: Let me let you answer the questions. And then we will see if--I have got seven or eight of us who have additional questions.

DR. CILLA: Okay. So you would like us to address those now?

DR. HENDRIX: If you could efficiently. Thank you.

DR. CILLA: We will do that. So the first question was, with respect to risk factors and looking at the skin adverse events. So we will address that efficiently. Oh; for RSV hospitalization. I apologize.

DR. GRIFFIN: Could I have ATM, please, Matt.

So we were able to get together some of the demographic factors for RSV hospitalization, the children who had breakthroughs and the children who didn't. Slide up.

[Slide.]

We looked at gender and race, ethnicity, age, weight, gestational age and chronic lung disease at prematurity status. There are some mild variations for each of these but the big difference, actually, is with the chronic lung disease of prematurity with over 45 percent having an RSV hospitalization versus 21 percent of those who didn't.

Slide off.

DR. CILLA: Another question you had had was regarding the dosing discontinuation for skin events. We have some information on that as well. While she is coming up, we did get the answer to one of the questions. There were no differences in the manufacturing process or facilities that could account for the observed hypersensitivity reactions.

DR. LOSONSKY: So the question was asked to show the patients who had discontinuation from dosing to look at severity and dose number to see if there was any pattern to those events by dose.

Slide on.

[Slide.]

So this is CP110. There were nine patients who had dosing discontinuation for a skin event. They all occurred within two days of dosing. These are the events, the severity of the events and when they occurred by dose.

I think it is very consistent with the data we showed in our dose number graph where it doesn't seem to be a pattern to the discontinuation of events by dose number.

DR. CILLA: Then the other outstanding issue we believe we have is to present the Southern Hemisphere severity of illness. While Dr. Griffin is walking up, I also wanted to point out that there is a notation on the FDA slide earlier about home use of palivizumab. We did want to correct that perception. It really isn't home use being administered by parents. There are health-care professionals that are in the homes administering the product and we just wanted to ensure that everyone knew that that was the case.

It is a very small fraction. In fact, less than 7 percent of the use according to a recent study is

administered by a health-care practitioner.

DR. HENDRIX: FDA, did you want to look at that.

DR. SHAPIRO: If you looked at the slide. Let's put Slide No--and the safety summary so let's go to Slide 52.

[Slide.]

We said, clearly, that it is home administration by health professionals. We did not say it was by parents.

DR. HENDRIX: Thank you.

DR. GRIFFIN: I am going to present the severity of illness by hemisphere, what we have.

DR. HENDRIX: Okay.

DR. GRIFFIN: Slide up please.

[Slide.]

Bearing in mind that there are only 15 patients in the Southern Hemisphere who had an RSV hospitalization, the first slide will show the percentage of patients who had an RSV hospitalization and needed additional support as I showed on the core presentation slide for all of the children in 110.

So you can see Northern Hemisphere here and Southern Hemisphere over here. Again, it is only 15 subjects in the Southern Hemisphere for the comparison.

Slide up, please.

[Slide.]

And now this looks at the duration of the RSV hospitalization supplemental oxygen ICU stay and mechanical ventilation. Yes; orange is mota--no. What? They switched it.

DR. CILLA: They switched the colors.

DR. GRIFFIN: Yes. Orange is pali. The colors previously had been orange--so they switched the colors. This was a quick slide job back there. So, anyway, we have got the colors switched but you can see the palivizumab, motavizumab, there doesn't seem to be a lot of difference with the small numbers in regards to severity of illness.

Slide off.

DR. CILLA: We believe that was it for our homework. Thank you very much for allowing us to present that.

DR. HENDRIX: Thank you for providing that. Dr. Freeman.

DR. FREEMAN: Thanks. Just one more question about the ADAs. I know some of this was in the material that we got previously to look at, but could you just review this a little bit about the data about the RC breakthrough and the presence of ADAs and if you have any information about the titers of the ADAS. Just thinking about it because it seems that there are more with that increase in ADAs, just to make sure it is not affecting the efficacy.

DR. CILLA: So you are specifically interested in hospitalizations by ADA positive or negative and, if we have titer information on those, we would go there.

DR. FREEMAN: Yes. Right. Thanks for phrasing that better.

DR. CILLA: We do have that. Dr. Griffin will address that.

DR. GRIFFIN: Slide up, please.

[Slide.]

So we did look at ADA and RSV events in the

children in 110, 124 and 117. And we combined the events, RSV hospitalization and RSV MA-LRI. You can see this is the total number of subjects who had the event in each of the studies.

We also looked at the number who had ADA testing performed and available. It was the majority of the subjects who had an RSV illness. Then, when we looked at the subjects who actually had an RSV illness with ADA detected, in 110, there were six out of the 68 who had the illness with ADA data available, six out of 68, in mota, none of the palivizumab group.

In 124, there was one patient in the palivizumab group, none in the motavizumab group. In 117, there were none who had an RSV illness with ADA detected. I think Dr. Robbie has the titers to present to you.

Slide off.

DR. ROBBIE: Slide on please.

[Slide.]

So this is a slide similar to what I had presented earlier where we have ADA on the Y axis, ADA titers, and 0

is without hospitalization and 1 is with hospitalization. As you can see, there are four individuals in CT110 who were ADA-positive and had RSV hospitalization. Their ADA titers are very much in line with ADA titers seen in patients without RSV hospitalization.

DR. CLAY: Would it be okay if I asked a question about your slide you just put up?

DR. CILLA: Would you like the slide back up? Thank you.

DR. CLAY: That one and 102 that you provided earlier. You have a very curious Y axis. That is not to scale. I am just curious. Did you design that for aesthetics only?

DR. ROBBIE: It is not to scale. It is just getting the titers.

DR. CLAY: No; I understand that, but in terms of it is not to scale, your distribution of your datapoints. So that is why I am curious. Did you design that one and the previous one just so you could fit them all on one, or did you look at it on a log-based scale to see if there was

a different distribution?

DR. ROBBIE: Yes; this is just so it can fit on the slide. That's all.

DR. CLAY: Thanks.

DR. ROBBIE: But the titers are listed here.

DR. HAGEDORN: Is it a log scale, though?

DR. ROBBIE: No; it is not.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: Hi. I was wondering if you could bring up--I'm trying to clarify something--the first or second slide from your homework where you brought up, I guess, the covariates looking at chronic lung disease as one of the risk factors for admission.

Just looking at the exclusion criteria that you handed out during the break, I just want to comment and ask why the 100 children with mechanical ventilation or other mechanical support were excluded when, on the spectrum of chronic lung disease, this would represent the more sicker end of the spectrum.

DR. CILLA: So it is how we developed our criteria

and why we are excluding those. So Dr. Losonsky will attempt to answer that question.

DR. LOSONSKY: Just to get a clarification. Do you mean hospitalized children on mechanical vent because there were children who did receive supplemental oxygen because they had E.T. tubes in and had that therapy at home.

DR. ZUPPA: So exclusion criteria that you handed out during the break said mechanical ventilation or other mechanical support including CPAP. So I am taking that to mean invasive and non-invasive mechanical support were exclusion criteria for these patients.

So, when you are saying that your part of the--but yet you are looking at a population with chronic lung disease. So, if you are excluding patients with both invasive and non-invasive support but have chronic lung disease, the patients that were included in this trial were on the less severe spectrum of chronic lung disease from prematurity.

DR. LOSONSKY: There were children in the trial who received supplemental oxygen, the E.T. tubes, at home.

DR. ZUPPA: Via tracheostomy tube.

DR. LOSONSKY: Yes. I'm sorry. Tracheostomy tube.

DR. ZUPPA: So they could have a tracheostomy but not require mechanical ventilation.

DR. LOSONSKY: Right.

DR. ZUPPA: So that was the sickest part of the spectrum of the chronic lung disease.

DR. LOSONSKY: Yes.

DR. ZUPPA: And then I have a couple of questions. I have been patient.

DR. HENDRIX: Okay.

DR. ZUPPA: For the 124, were patients with mechanical ventilation--so there are a lot of patients with chronic lung disease who have congenital heart disease or vice versa. Were patients with really bad CHD--were they mechanically ventilated?

DR. FELTES: Hi. I am Tim Feltes. I am a pediatric cardiologist at Ohio State. It is a great question. The main reason why we excluded kids who were

currently in the hospital on mechanical ventilation was that we wanted these patients to be exposed to community RSV. Those patients certainly would have been candidates to enroll if they were on the verge of discharge from the hospital.

So we, indeed, wanted to include those kinds of sick children but we wanted to look at community-acquired RSV rather than nosocomial.

DR. ZUPPA: You could be home on a laptop ventilator with a--

DR. FELTES: Right. No; I'm sorry. Maybe I misunderstood your question. A child who is on a chronic home ventilator could be enrolled.

DR. ZUPPA: That is not consistent with the exclusion criteria that we were handed. What is it for 124 or for 110? 110, it says clearly, that mechanical ventilation or other mechanical support was an exclusion criteria.

DR. FELTES: I'm sorry; I am talking about 124.

DR. ZUPPA: 124. Those children could be

enrolled.

DR. FELTES: Yes.

DR. ZUPPA: So then I am just trying to get to, I guess, Slide 28 which I guess one of the stronger points of your application speaks to the patients with RSV hospitalization requiring additional support. You just showed a slide breaking down the geographic distribution of these inpatients.

But do you have any more information about these patients that were hospitalized with regards to whether or not they had chronic lung disease or not? I am just trying to think of the population that would benefit from this therapy.

And it was remarkable to me that only 50 percent of these patients needed supplemental oxygen whereas I would think that would be one of the strongest indications for admission to the hospital especially when we are seeing such a low rate of hospitalization.

DR. CILLA: So you asking if we have conducted the severity-of-illness analysis by population type CLD and CLD.

DR. ZUPPA: Correct. I just saw the geographic breakdown slide but I haven't seen any more breakdowns in terms of demographics.

DR. CILLA: Unfortunately, we don't have that information.

DR. ZUPPA: Okay.

DR. HENDRIX: Dr. Havens.

DR. HAVENS: Thank you very much. So I wanted to clarify a couple of issues. First of all, the Hexaplex was used initially but then it was changed to a new test. I assume that the data that we are looking at have all been retested with the RT PCR. Is that an accurate statement?

DR. O'REAR: That's correct. The sponsor went back and retested all the samples.

DR. HAVENS: Okay. And then, in terms of the geographic variability, a question for the sponsor, in the background information figures 6.1.4-1 and -2, you show, for North America or the United States, those n's are only slightly different, that there is really--well, the relative risk is right on 1. So it would be hard to say that you are

getting much benefit in that population.

And then we compare that to the data presented a slightly different way by the FDA looking at the Northern Hemisphere and the Southern Hemisphere but recognize there is something different about hospitalization.

Combining the MA-LRI and hospitalization groups is not exactly legal and so I hesitate to ask you to do it except you just showed a slide where you did it. You did have a slide suggesting that you thought it was going to be okay, your Slide 29 where you showed that the subset populations were similar to the non-subset populations.

So my question is what was the geographic distribution of the subset versus non-subset populations before I ask you about did you combine those.

So, were there more non-subset populations in the Northern Hemisphere?

DR. CILLA: So the geographic distribution of the subset populations.

DR. HAVENS: Yes.

DR. CILLA: I believe we can pull that one.

DR. HAVENS: I am trying to give you every possible chance to get to show me the mota versus pali overall effectiveness. I am trying to find some overall effectiveness subtracting out--the basic problem with the study is you have a physician-derived variable as your endpoint which is, am I going to put you in the hospital or not.

So, if we just take--everybody came to the doctor from RSV, at least we can try to get some sort of feeling for that. But then you have to--I mean, that is why you started with the MA-LRI stuff later, I assume, because you saw it was a big deal.

So, if there is a way to combine those, that would be interesting for me to see although we would look at it very carefully. But then one of the questions is if there is a big difference in the geographic distribution of the Northern Hemisphere and Southern Hemisphere with your subset versus non-subset population. So that is the first place to start; subsets, by geography.

DR. CILLA: Please respond.

DR. GRIFFIN: Okay. Slide up.

[Slide.]

So this shows the subset and non-subset sites by countries here for North America, European Union, rest of the world, Northern Hemisphere and rest of the world, Southern Hemisphere.

There were more countries in the non-subset population or more sites over here but a representative group in the subset.

Slide off.

DR. HAVENS: Okay. When you look at the RSV-related outcomes of either hospitalization or MA-LRI, could you show us the equivalent of Figure 6.1.4-1 or 6.1.4-2 for those combined groups which is the overall relative risk.

DR. CILLA: So you are looking for forest plots of the overall relative risk for a combination of hospitalization and MA-LRIs?

DR. HAVENS: Yes. Did you do that?

DR. CILLA: I am asking right now. If you will allow us just one moment to confer. So, I am told that we

do not have that by RSV-specific endpoints.

DR. HAVENS: So then, if I happen to practice in North America or even the United States, then, when I am trying to figure out if this is reaching the point of noninferiority, if I look at the plot 6.1.4-1, it is right at 1.

DR. CILLA: So you are saying is the relative risk comparable to a highly active agent in hospitalizations.

DR. HAVENS: Well, this makes it look, for hospitalization, like mota equals pali, exactly.

DR. CILLA: For hospitalizations.

DR. HAVENS: For hospitalization in North America. Now, the other stuff makes it maybe look like it might be better for MA-LRI but you look at that together. So it is hard to see where it would all sort of sort out.

If we think that, in the United States or North America or Northern Hemisphere, we are less likely to hospitalize. People don't really need to get in, although, if only 50 percent got oxygen, you can ask a lot of questions about why they got in to begin with.

Okay.

DR. CILLA: Okay. The short answer is, Dr. Havens, we agree with you that, in the United States, motavizumab is approximately equal to palivizumab with the exception of MA-LRI where it looks like it is greater and then, certainly in other countries or other areas of the world, it looks like it actually performs a little bit better.

DR. HAVENS: Well, it is not noninferior.

DR. CILLA: Yes.

DR. HAVENS: Which is a long way from "performs a little better." But, okay. So, then, the FDA quotes a statistically estimated three-fold increased risk of high-grade hypersensitivity that was based on that one table where there was 19 versus 0. And when I asked about the bottom-line statistics, they said, if we subtract out everything, about a three-fold increase.

Now, I am interested in the sponsor's response to that. On your Table 7.4.8.1.4.2-2--you didn't think I could do that.

DR. CILLA: No; I didn't.

DR. HAVENS: You look at a similar problem which is skin events within two days and it includes things like urticaria and it is within a short time frame after we got it so we could all, perhaps, believe that these were really related to drug administration acutely.

If I look at the two groups that you lumped together there--you may have a slide on this--it seemed like excluding the Indian group, which I think is different because they had an IgE-related--they had the only IgE-related response. So I don't want to look at them. But just the other two, it seemed like there were nine versus 29 which would, again, be this kind of three-fold increase in hypersensitivity that we might believe in.

And I just need your sense of what you really believe is the bottom line for this kind of either skin rash or skin edema kind of--and within a short time frame so we could really think it might be infusion-related or drug-related--if you think my analysis of that nine versus 29, which is about three-fold--or if you have a different

summary statistic for that kind of adverse event or hypersensitivity.

DR. CILLA: So just to ensure we are on the same page as you, can you confirm that the table number is 7.4.8.1.4.2-2?

DR. HAVENS: Yes; I can confirm that right here.

DR. CILLA: Perfect.

DR. HAVENS: And that is on Page 113 out of 147 in the Backgrounder Information.

DR. LOSONSKY: So Slide on for everyone who doesn't have that memory to remember those numbers.

DR. HAVENS: Oh; I wrote them down.

[Slide.]

DR. LOSONSKY: This is the table. Basically, when we look at those events--and these would be events that would be captured by the angioedema anaphylaxis, SMQ, the non-specific events which we can't characterize. It may have some hypersensitivity events in there, but our overall assessment of the non-specific rashes, even within two days, was they had low rates of recurrence. 90 percent didn't

recur.

So, when we look at these, we get for CP110 rates of 0.7 versus 0.2. It is not that palivizumab doesn't have reports of urticaria within that time period or events that might be consistent with an allergic reaction, but there is a higher rate as you pointed out, Dr. Graham.

DR. HAVENS: Right. So here the specific events less than or equal to two days of dosing, if you took 110 and 124, that would get you into a similar range. So you have 8 plus 1 is 9 for the pali and 23 plus 6 is 29 for the mota of those specific events that we might agree were not these random rashes that occurred distant from the dosing or in general. Is that--

DR. CILLA: Yes. I think we would agree with that.

DR. HAVENS: Thank you. I have one more. Oh; I'm sorry. Actually, this one is for the FDA. Should I wait on that one?

DR. HENDRIX: Why don't we wait on that one. I have got four more here that are going to ask questions. I

would like to ask that these be targeted in clarifications because, then, what we are going to do is we will go to the charge and we will do each of those in turn.

We have had a very wide ranging discussion in pairs here for an hour or so. But I want to make sure we get back to schedule. Dr. Hagedorn is next.

DR. HAGEDORN: I had a question regarding the CP110, premature infants, the severity of illness in patients that were hospitalized. If you look at those numbers on mechanical ventilation and ICU stay, they look really tantalizing and interesting.

Are these numbers--is this a subset of the total group of patients in CP110 or approximately how many patients are involved in there. If those numbers within the bars are representing patients, it is a very small subset.

DR. GRIFFIN: Slide on, please.

[Slide.]

These are all of the patients in 110 who had an RC hospitalization, 62 in the palivizumab group and 46 in the motavizumab group. Those were all of the RC

hospitalizations in 110. The numbers inside the bars are the actual numbers of patients.

Is that helpful?

DR. HAGEDORN: So there was only a total of 12 or 13 patients that ended up on mechanical ventilation out of the entire population of patients studied; is that right?

DR. GRIFFIN: That's correct. Well, out of the patients who had an RSV hospitalization.

Slide off.

DR. HENDRIX: Dr. Luque.

DR. LUQUE: Could you comment on the sensitivity of the test that you used for anti-drug antibodies?

DR. CILLA: Yes; we can. I would ask Dr. Robbie to provide the answer. I don't know it specifically.

DR. ROBBIE: Slide on, please.

[Slide.]

Okay. The assay that was used for measuring ADA for motavizumab and palivizumab was a sensitive and robust drug-tolerant assay. We can measure very low concentrations of ADA in the absence of drug, for example. We can measure

up to 3 to 5 ng/ml of motavizumab and up to 3 to 6 ng/ml of ypalivizumab.

In the presence of about 100 micrograms/ml of drug, motavizumab or palivizumab, we can measure very low levels of ADA which is less than 250 ng/ml. By the way, this 100 micrograms/ml concentration is the mean concentration that was observed at that trough sample which was collected.

At the top end, we have some patients with high concentrations of up to 300 micrograms/ml of drug. In the presence of even these high concentrations of drug, we can still measure low single-digit microgram/ml concentrations of ADA for both motavizumab and palivizumab. This assay is also very specific and, overall, this is a very robust assay and we are fairly confident.

DR. LUQUE: How long out can you detect levels of ADA? I mean, for how long do they persist?

DR. ROBBIE: Oh, persistence of ADA. The measurements were done on day 120. It is a single time point for the three different studies, so we haven't

followed persistence of ADA, unfortunately.

DR. HENDRIX: Dr. Maldonado.

DR. MALDONADO: Unfortunately, I have four questions but they are fairly focused. I think they are pretty, hopefully, yes or no.

Let me start with a couple of resistance questions. So I am looking at the background document you had on Page 27 of 147 on Section 2.3 where you talk about motavizumab epitope and viral resistance. You talk about the 13 amino-acid sequence that is specific to this product.

I am wondering if you looked at those epitopes. I think this question might have been asked in a different way but has anybody looked specifically at whether any of those particular epitopes are associated specifically with hypersensitivity any way in vitro or in mice--maybe not in vivo, but in mice, anyway.

DR. CILLA: I will ask Dr. Suzick to answer that question.

DR. SUZICK: We used in-silico modeling to estimate the number of human T-cell epitopes present in

motavizumab and palivizumab. They had about equivalent numbers of potential T-cell epitopes. But we don't know whether those actually manifested T-cell responses in vivo or not.

DR. MALDONADO: Okay. And then the second resistance question, then, is, in the same section, you talk about resistant patterns and there is possibly one substitution that might be related to resistance. But it wasn't present in immuno-prophylaxis-naive patients. Was it present in any of these kids?

I think you said it wasn't present in failures, but I just wanted to see if it was present in any of the other patients.

DR. SUZICK: Slide up, please.

[Slide.]

As has been discussed previously, both motavizumab and palivizumab bind to a highly conserved epitope on the F protein called the antigenic A site. All resistance mutations that have been mapped on the F protein. All the mutations in RC that render the virus resistant to mota and

pali have been mapped within antigentic Site A.

So we looked at 115 different breakthrough isolates collected from palivizumab recipients, 114 from mota recipients, and looked specifically for changes within antigenic Site A.

You can see the changes that were observed and the total numbers that were observed among the isolates we were able to sequence. So there were about 6 percent of the breakthrough isolates that contained a change in antigenic Site A among the palivizumab breakthrough cases. When we looked, all of these generated resistance to palivizumab.

Among mota recipients, we saw similar changes within antigenic Site A. However, changes at these positions rendered virus still sensitive to motavizumab and it was only the change at K272E, only that single change, that gave rise to resistance to motavizumab.

When we looked among isolates collected from subjects who were not undergoing immuno-prophylaxis with either mota or pali, we saw a very low rate of changes within antigenic Site A and we never observed the K272E

mutation. That was only observed in immuno-prophylaxed individuals.

Slide off.

DR. MALDONADO: Thank you. Then, briefly, there are two clinical questions, again bringing the issue back to understanding how this would compare to palivizumab in terms of clinical utility.

So you mentioned that a degree of chronic lung disease--I'm sorry; you talked about chronic lung disease versus non-chronic lung disease in terms of outcome measures. Was there any clinical data available in terms of stratifying lung disease, so more severe, less severe, baseline O2 use or degree of O2 use, anything along those lines that would at least allow you to stratify which patients might be at higher risk for disease or have a better outcome if this drug were used in that population.

DR. GRIFFIN: We just stratified by the presence or absence of chronic lung disease, so we don't have any other information on that.

DR. MALDONADO: Okay. Then the final question and

I assume it is going to be a very similar answer, but I will ask it anyway. In terms of outpatients, I know you looked at outpatient disease. So I am wondering if there was any measure of looking at antibiotic usage as an outcome as well.

So were patients who got your product less likely to have antibiotics in an outpatient setting compared to those who didn't?

DR. GRIFFIN: There were a number of non-specific, non-RSV-specific secondary outcomes. Slide up.

[Slide.]

And antibiotics was one of those. We actually looked at antibiotics for outpatient MA-LRI and otitis in 110, and you can see that there was no difference between treatment groups.

Slide off.

DR. HENDRIX: A follow-up question to that, Dr. Freeman?

DR. FREEMAN: Did you look at inhaled beta agonists or steroids or anything as well as antibiotics, or

just antibiotics?

DR. LOSONSKY: What we looked at was the use of bronchodilators or steroids for RSV MA-LRI in children who had outpatient events and the rate was very high, 70 to 80 percent. So if you actually had an RSV event, there was a high rate of bronchodilator or steroid use.

DR. HENDRIX: Dr. Graham.

DR. GRAHAM: I wondered if any of these children were followed up in the second year of life to see if they had RSV-specific antibodies and whether it would give you some sense of whether infection was prevented altogether or whether you just created subclinical infection.

DR. CILLA: So the question is did we follow up any of the patients who didn't participate in some of those studies where we had two seasons; correct? Okay.

DR. LOSONSKY: If I understand your question, you wanted to know did we specifically follow up the motavizumab or palivizumab patients through a second year, looked for a generation of anti-RSV antibody? No; we didn't do that, although we believe, based on the activity of palivizumab

and motavizumab, that we wouldn't be expected to prevent infection but rather prevent the severity of an illness.

There have been post-approval studies of Synagis trying to address that question looking for--trying to answer the question, are there increased rates of RSV then in the second year in these high-risk infants. In those studies, the answer was there was no evidence that there was.

DR. HENDRIX: Peter, did you have a last question for the FDA? I have one final that I will have for the sponsor. Go ahead.

DR. HAVENS: I just had a question for Dr. Birnkrant if that would be okay. Is that okay?

DR. HENDRIX: Okay.

DR. HAVENS: Well, at the beginning, you made an unusual statement about a newspaper article which I had not--

DR. HENDRIX: Well, where is this going? I mean, is this--

DR. HAVENS: I just wondered if--she brought it

up. I wondered if understanding that would help us in our deliberations. That is the bottom line.

DR. HENDRIX: Okay. I will let her answer, but I don't want to get into a discussion unless there is concrete data that we have to go over with this because I don't want to confuse our deliberations based on the data we--

DR. HAVENS: No; absolutely.

DR. HENDRIX: Okay.

DR. HAVENS: But just to try and understand if there was something there that would should know, about as we think about this if it was materially pertained to this or not. That's it.

DR. HENDRIX: Okay.

DR. BIRNKRANT: It is my understanding, based on what was in the public domain, that there were questions raised about the conduct/analysis of testing, in particular looking at an immunofluorescent assay and the sensitivity and specificity of that assay and, perhaps, other related assays and that data collected in one lab in California may not have been the same as data re-run in a lab in

Gaithersburg.

That is about all of the information that I have. My information is really based on the article that appeared on Friday as well as the complaint that is also available in the public domain.

So we have not had a chance to discuss this directly with the company. However, we would like to understand further what the allegations mean and what the actual discrepancies are and just to understand the whole situation a lot better.

Once we have that information, we will gladly share it with the advisory committee. I don't know if the company wants to make a brief statement.

DR. CILLA: We certainly would. And we would ask that an individual from the sponsor section outside of the bullpen be allowed in to make a comment.

DR. HENDRIX: That would be fine.

MS. JALLAL: This is Bahija Jallal, Head of R&D at MedImmune. Thank you for the opportunity. MedImmune is confident that the data which was presented to you today and

also in our CRL and also in our BLA are accurate. The pending lawsuit contains unsubstantiated allegations by a former employee and MedImmune is confident that all the data that were submitted for review, we stand behind them and that they are accurate.

DR. HENDRIX: Okay. Thank you. Let me take my turn to ask a question. This is a two-part question for the sponsor. Were there any analyses of the primary outcomes in which mota was superior to pali. And the second question that is related to that is, if the outcome of the FDA's final decisions after deliberations are to grant marketing approval for mota, what are the plans for pali in the future?

DR. CILLA: Why don't we address the first question about any primary outcomes which were superior.

DR. LOSONSKY: In CP117, the placebo-controlled trial, there was superiority.

DR. HENDRIX: Head-to-head. I should have been more specific. In the head-to-head trials.

DR. LOSONSKY: I'm sorry.

DR. HENDRIX: I wasn't specific.

DR. LOSONSKY: The outcome was noninferiority. So we met the noninferiority outcome for the primary endpoint for hospitalization due to RSV.

DR. HENDRIX: So the follow up to that, then. The statement in the concluding slide from I think it was Dr. Geba about mota being the agent of choice was based on which data that was presented from the head-to-head comparisons with pali?

DR. CILLA: We would ask Dr. Losowsky to answer that question as well.

DR. LOSONSKY: So, looking at the totality of the evidence of the noninferiority outcome in RSV hospitalization, the point estimates were all in favor of motavizumab. The secondary endpoint, which is a supportive endpoint--slide on, please.

[Slide.]

So the secondary endpoint, which is here, which actually showed, demonstrated, a superior outcome for the secondary endpoint in CP110. And the consistency of that

data supported by 117 leads us to believe that this is potentially a better product for the prevention of serious RSV disease.

DR. HENDRIX: Okay. So then the question 2A that I asked earlier then would be the plans for pali after, assuming that mota is granted marketing approval.

DR. CILLA: So MedImmune--obviously, our top priority is to make the best immunoprophylaxis available to children who are at high risk of RSV disease. So it is anticipated that both motavizumab and palivizumab will be available in the marketplace at market introduction.

Now, the duration of overlap of those two would depend a lot on what is actually included in the motavizumab label, the emerging safety profile occurring as motavizumab hits the marketplace as well as physician-use patterns.

DR. HENDRIX: Thank you very much. At this point, given the time--I have got 2:37 on the clock--I am going to turn this over now. We will go ahead and proceed with the FDA charge to the committee from Dr. Birnkrant.

Charge to the Committee

DR. BIRNKRANT: Thank you. This will be brief so that we can get to the questions. I think it is quite obvious to everyone in the room that this was quite a complex biologics licensing application.

Number one, it was quite large. The principal clinical trial had over 6,000 subjects enrolled. In addition, it was as though 2 BLAs were presented to us and two reviews were conducted. We had the original submission where we noted that there were data deficiencies; that is, we needed more information to be able to continue our review.

Our requests for additional information numbered 40 and included not only clinical but microbiology as well as chemistry, manufacturing and controls questions. I want to thank the applicant for putting together such a complete response to us.

So then we had to review almost the second BLA because not only did we have to review the data based on our questions that were sent to the applicant but there was a new trial in there, CP124, in congenital heart-disease

subjects.

In addition, as you can glean from the discussion, there were a lot of questions with regard to the assays, not only the assays for local testing of RSV as well as anti-drug antibody assays. So we had to get a handle on that and we appreciate the sponsor's help in that.

In addition, when it comes to safety, based on the patient populations enrolled in these trials, they were very high-risk subjects. So, as you can imagine, it is quite difficult to ascertain events that are due to the drug versus background rates. So that was another challenge, I believe, for both the company and for the agency.

So, with that, I would like to turn to the questions. You will see that we pose the safety question first, which is a little unusual. But, nonetheless, we wanted to get active discussion and a read from the committee before we proceeded to the other questions for discussion and voting.

As was mentioned and discussed, I think extensively, we are concerned about serious skin reaction/

hypersensitivity/suggested anaphylaxis cases. So, again, that is another reason why we are putting forth the safety question first.

Thank you very much for your deliberations.

Questions for Discussion

DR. HENDRIX: So I am going to read this question into the record and then I will open the discussion for this specific question. Then we will do them in turn.

No. 1; please comment on the safety profile of motavizumab specifically with respect to the potential for hypersensitivity reactions including life-threatening anaphylaxis.

So we will now begin the panel discussion portion of the meeting. All of this portion is open to the public observers. Public attendees may not participate except at the specific request of the panel.

So this question is now open for discussion of the committee. You are all talked out. Dr. Ellenberg.

DR. ELLENBERG: In reviewing the--one of the concerns is when you see some level of reactions in a

clinical trial, you think about what might happen if this were out in the public. That was why I had asked about the exclusion criteria earlier.

Looking at these exclusion criteria, it does seem to me that there are portions of the community of kids who would get this who are sicker than the kids in this trial. The CP110 excluded children who had a life expectancy of less than six months who were on mechanical ventilation, who had known renal impairment, who had known hepatic dysfunction.

I don't know whether any of those conditions would increase the chance that they have a hypersensitivity reaction. I am not a clinician so I will have to turn to the rest of you, but whether, if they had a hypersensitivity reaction, whether they might--the consequences might be more severe in children who were sicker.

So one thing that I worry about is whether, even if we didn't have deaths in the study or the grade 4, the life-threatening events, whether those might happen out in the community in the larger population.

DR. HENDRIX: Dr. Maldonado.

DR. MALDONADO: I would like to echo those comments. I do think one of the major concerns here is that the background signal here, even in this--I am sure it is a big number but, in terms of looking at the risk of adverse events in the larger population, I don't think we are going to pick up the signal here.

So my sense is that there will be a much brighter signal when and if this goes to phase 4, and that is a concern. So I think that some of the issues around understanding or drilling down a little better in terms of what would be the power of these observations in a larger sample size and what is the power now. I suspect the power is pretty low at this point.

We face these issues with vaccines as well, obviously, and so we know all too well that we have to keep close track. I know the VAERS system quite well. I don't know what phase 4 system the FDA or others would have to do this kind of tracking or for, say, the sponsor to go back and drill down further on safety and stratify even more,

although, again, I don't think you can do it with this relatively small number of patients in this relatively rare side effect.

So that is the major concern, I think, for me.

DR. HENDRIX: Dr. Cargill.

DR. CARGILL: I would expand upon those and say that, in addition to that, while we have had data on the ADA, we do know that 17 out of 58 of those had reactions.

The other concern I would echo and amplify upon is, when trying to discern what was underneath that, we had data that took us in two different directions. We had some of that, because of either gender or ethnicity and others with a family history or non-family history of atopy.

I think we take a look at these numbers, then imagine going into even larger numbers, what that would mean.

DR. HENDRIX: Dr. Roland.

DR. ROLAND: I find it really challenging to consider the questions of safety and efficacy completely separately and to consider the relative safety of the

product that is on the market and the product that we are asked to consider now.

So, if we have a product that is efficacious and safe that is currently on the market and now we are looking at the product that has the potential for a new serious adverse event, that is the primary concern for me particularly when we are not looking at a product that has evidence of superiority in terms of efficacy.

DR. HENDRIX: Dr. Clay.

DR. CLAY: I will just echo your comments there in comparing the safety of the two drugs. Hypersensitivity and skin issues aside, I am not really seeing a difference. I would like to have seen a difference.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: Again, just to echo. So we have a history with palivizumab in patients who are sicker than the patients who received this drug with a pretty good safety profile and, again, what everybody is saying, these patients in the spectrum of chronic lung disease were not that sick. And yet there was significant safety concern.

So I wonder if moving forward in patients who were sicker, actually, got the drug would have had--if we would have seen more adverse events.

DR. HENDRIX: Dr. Strader.

DR. STRADER: I would like to present a slightly opposing point of view. As a clinician and an adult clinician, I always think it is preferable, because I deal with biologics as well, to have a choice in the medications that we use.

This trial appears to me to have been set out to show noninferiority or at least equivalence. So I think it is slightly disingenuous to expect things to be better when what they are trying to show is that they are noninferior, or at least equivalent.

The side-effect profile that we see here is of some concern. Not being a pediatrician, I don't know how much of an issue it is to have urticaria and grade-3 skin reactions in children. But they all seem to have been reasonably well-managed, identified reasonably early and I think that the opportunity to have another medication that

could potentially be of benefit in a disease that is severe is probably a good thing.

My personal opinion would be that I think that there is more data that needs to be followed to make sure that we don't get into trouble in the future.

DR. HENDRIX: Dr. Clay, you wanted to respond to that?

DR. CLAY: Yes. I would like the option as well. But, in looking at these two drugs, what would be the criteria by which you would choose one over the other as they stand right now?

DR. STRADER: As a clinician, the opportunity to have choice is a good thing. I mean, I don't necessarily--if I am choosing, for lack of a better example, a proton pump inhibitor, I don't care whether it is this one of that one as long as I know that they both have equivalent activity and that, if there is a difference in side-effect profile, it is not a huge difference that is going to change my mind one way or another.

So this is just coming from a clinician's point of

view. This is how I would view whether or not to make a decision in this area.

DR. CLAY: So, basically--in other words, there wasn't anything that you saw that said, in this patient population, in this one I would choose that one.

DR. STRADER: No.

DR. CLAY: Okay. That is what I was--great.

DR. HENDRIX: Dr. Ralston.

DR. RALSTON: So I am a little stressed by the question in general because I am new to this process and a little bit unsure. But when I heard the motavizumab as the drug of choice, it made me doubly stressed because I wrote down, not superior, questionably noninferior, and concerned about side effects.

You could market a drug as noninferior but I am unsure what our role is if the intention is to market this drug in place of palivizumab, or the intention is to market this drug as better. That disturbs me. I am stressed by that.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: Again, I want to stress--I mean I am a pediatric critical-care doc. We have a 45-bed ICU. I can tell you, in a season, we easily intubate more than 13 children for RSV infections who do not have a history of prematurity or chronic lung disease. They are well kids who got RSV in day-care.

I mean, we might do that in a month. And that is just at our institution. So I am perplexed by--in this entire study of the patients that were hospitalized, there were only 13 patients who were mechanically ventilated. I don't understand that. I don't know if we can say that this population was just not that sick to start with?

But then, again, I mean we have children that are well with no past medical history that get intubated. So that is concerning to me. So to see this adverse-event profile--I mean, the thing with urticaria and hypersensitivity in kids that are sick with congenital heart disease or mechanically ventilated, you have no idea what is going to happen. How is a sick heart going to take a hypersensitivity that is escalating into true anaphylaxis.

Are you going to go into distributive shock? Are you going to kind of just respond to your IM solumedrol and your inhaled beta agonist? Who knows?

But then, again, some of these therapies that are used to treat the adverse events, so the beta agonist is going to increase your heart rate. Is a kid with congenital heart disease going to tolerate that?

It just leads into the more you do, the more you do. So that is my--I don't understand the data. It doesn't make sense to me. And that is my biggest concern.

DR. HENDRIX: Dr. Havens.

DR. HAVENS: Well, one of the questions came up, what would differentiate mota from pali. I think some of preclinical stuff that looked really very exciting is it might actually be better, that it might be more potent. But then you can't see that in a study that looks at such a relatively healthy population.

But when you look at the days in the ICU or total mechanical ventilation, it does suggest that mota might actually be more potent.

When you look at the issue of the safety profile, you could argue in a group of healthy children like were studied here, this amount of increased safety risk is not worth the potential for what little extra benefit you might get in this group.

If they redid a study in a group of patients who really needed it, it might be a smaller group but you might see a bigger benefit perhaps, then, in terms of intubation or even in the way of therapy.

And then the increased risk of hypersensitivity might actually be worth the potential benefit. So I agree with the people who are saying they might want to have two drugs. The way you choose between these two drugs now would be based on you wouldn't want to use mota in somebody who fell into a relatively low-risk group. You would use pali because it has less risk of hypersensitivity.

But then, if you had a really sick patient, you might take the risk of worse hypersensitivity response rate because it might actually be a better drug. Unfortunately, we don't get to see the data partly because of the

difference or the relatively non-sick population that was studied.

DR. HENDRIX: Dr. Hagedorn.

DR. HAGEDORN: I would just like to emphasize that--we didn't discuss this in detail, but scientific rationale for taking mota forward in the clinical trial looked pretty compelling. I think one of the challenges is this is a very difficult problem to do careful clinical trials and come up with a very clear answer.

So, regarding Doris's point of having different options for some subsets of patients is worth considering.

DR. HENDRIX: Dr. Atkinson.

DR. ATKINSON: Well, I am an allergist. I am convinced, just looking and listening to the reactions, that some of the--at least some of them do have an immunologic basis. It does seem likely--and some of them have been fairly severe--it does seem likely to me that if the postmarketing study--if the drug were to be approved for use and postmarketing studies were to be done, that they would probably be--we would probably get some even more severe

reactions.

But we might also see that, actually, it is more effective if we could get some more data on hospitalizations. So the fact that there weren't any deaths directly related to the product and that none of the reactions reached actual full-blown anaphylaxis is kind of encouraging.

So I think that, with some restrictions on postmarketing use, it could be considered to be approved with careful monitoring based on the fact that we really don't have enough data to say that it isn't--there were trends that seemed that it was potentially a little more effective in preventing hospitalization but, from all the data, all you can say is it appears to be more or less similar to the comparator.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: With regard to the issue of choice, I would just sort of refer to the question that the chair asked. In general, I am very supportive of having choices. I have spent a lot of energy trying to explain to

people why the FDA doesn't always require a new drug to be better than old drugs. It is important to have choices.

But here I wonder whether there will be a choice. Generally, a choice means you have products maybe in two different classes or they are made by different manufacturers and more different than these two drugs are.

I, too, wonder about the future of pali if the manufacturer believes that mota is the treatment of choice. I don't know how long there would be a choice between the two of them.

DR. HENDRIX: Dr. Maldonado.

DR. MALDONADO: So I think that--I was actually just going to say I agree that I am not sure that we can address choice here because it is not really up to us and it may not be a choice.

But I also think that, again, as clinicians--I am a peds ID person. I am also the head of infection control at my hospital and I can tell you, as the others have said, it is a tremendous disease. I think it is very difficult, in this day and age, with the sick kids we have, to really

learn how to prevent this disease even better would be a fabulous thing to do.

I think there is a lot of promise here. I think some of us have echoed that already. There is just this tease of, probably going to be better, could be better. And I am specifically coming to the point of safety because we can't do cost/benefit unless we really understand what the cost is going to be here, and that is what the safety profile is.

So, the benefit depends, as was pointed out, on how much the cost will be to us. I think that we have asked some questions today which would give us a pathway to understand exactly how do we stratify these sick patients. Do we need sicker patients? And all of that entailed in terms of additional clinical trials versus moving on to phase 4. Those are difficult things to consider for industry when these are kids who are already very high risk and may be hard to enroll.

But I don't think, with the data that exists, it is going to be easy to answer this unless you try to do it

in a very complex cost/benefit model which I don't think will convince a lot of people and we may get ourselves back into the whole issue of whether we should be using--how we got into the whole ribovirin issue back in the '90s or even when we started with the original product the sponsor has on the table now.

I think we need to get more information, whether is pre-licensure or post-licensure. I don't think we can answer the cost/benefit question at this point with the data that is available.

But there are potentially easier questions that can be answered that maybe are either in the database somewhere and need to be pulled out or just weren't asked and maybe have to re-asked in a different way.

DR. HENDRIX: Dr. Veltri.

DR. VELTRI: I think you can only work with the trial design in a population and the results and what was available at the time. I think the sponsor and the FDA have collaboratively done their best to try and get an answer here.

Clearly, it looks like, from an efficacy perspective, it is noninferior and there are some trends here and there. It may not be optimal population now. contemporaneously, and more data is required.

Certainly, from a safety perspective, there clearly is a signal. It is rare, but it may get more widespread. I think that these are things that can be further elucidated through further studies in higher-risk groups, enriched groups, and certainly through labeling.

I am a little concerned, when the industry does work and they find a drug that is effective and there is a safety concern, throwing out the baby with bath water here. In this particular case, I think option is good. We can't say anything about cost or what have you, but there could be patients who would benefit from this.

My concern would be that the hypothesis testing has given us some answers. There is a lot of hypothesis-generating information now. I think that just tells us we need more information.

So I think it is benefit/risk is what it comes

down to.

DR. HENDRIX: Dr. Roland.

DR. ROLAND: I appreciate the last comments. It is really difficult to be in a position of seeing so much effort and promise. But this is also a regulatory role that we are in. We have to provide advice based on an absolute unknown. I think the fundamental question is are we comfortable advising you to take the chance of figuring it out out there in the real world or do we want to err on the side of caution and say, that is too risky.

If the sponsor wants to gather more safety data, you look at it again. I think, to me, that is the fundamental issue. We do not know what the true risk is and there is a signal that it could be significant.

DR. RALSTON: I am still struggling with the heterogeneity represented by the Southern Hemisphere data, too. We keep saying that it is noninferior. I don't know that I believe that. That is my one point.

My second point is I think that, since the prevention of hospitalization is our primary endpoint, one

of the things that you want to think about from a clinician's perspective, the severity of the skin reactions that were required are the kinds of things that I get asked to hospitalize children on a regular basis.

If you applied that across the board to a sicker population, I suspect that we are going to be hospitalizing children for some of these skin reactions. As a comment.

DR. HENDRIX: Dr. Luque.

DR. LUQUE: I completely agree with your statement. I think they haven't proven with the data that have been shown that it is noninferior, at least not for the entire study population that they presented. So, based on that, I think we need to request more information because the medication seems to have immunogenicity that we cannot simply ignore.

I think it has the potential for severe adverse events and, in sicker children, it is going to be worse.

DR. HENDRIX: I am going to summarize the comments for this and then we are going to go on to the next question. This is not in any particular order, but if I can

make some sense out of this.

There are a number of comments that there was a clear signal, although it was rare, but significant when it occurred. We heard from the immunologists that it did have a characteristic, at least in some of the cases, of an immunologic basis. But there was also the thought that, with certain restrictions on use and labeling, it may be managed in a reasonable way to avoid some of the toxicities.

There was a pretty consistent call for needing more information. But the issue is whether the information is to be gathered this side or that side of marketing.

Another sort of general theme had to do with the populations where, if there were a sicker population, it might be a different weighing of the hypersensitivity risks that are described. If it was a larger benefit in sicker kids that would be studied as it seemed that there were a couple of comments about the lack of very sick kids that were in this that may be somewhat atypical, at least in the practices of those that are involved here.

So I think those were kind of the main points. I

should also say there are number of people who voiced comments that it is useful to have options. I will leave it at that.

So I will go ahead and read the second question from FDA; do the data from the applicant's studies adequately support the efficacy of motavizumab for the prevention of serious lower respiratory-tract infection with RSV in at-risk infants.

So we will go ahead and open the panel discussion and, again, I will mention, regarding public observers and attendees, that you may not participate except at the specific request of the panel.

So this is open for panel discussion now, Question No. 2.

DR. CLAY: I think, in 117, it clearly showed that it was effective in preventing RSV hospitalizations in the Native American population. The issue I had with that one was you don't know if it is any better than what was previously shown in IMpact and Cardiac studies even though those are very different populations.

But, in that one population, yes; I think that is pretty clear.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: I am comfortable believing that this is an efficacious product. I, too--you can't help notice--it was certainly brought to our attention, the big push from the Southern Hemisphere data. But it is certainly also true that when you look at that lots different ways and you chop them up and look at different subgroups, it is not surprising to find a subgroup or two where the results look quite different.

Generally, I am inclined to believe, if the population, itself, you had reason to expect things to work pretty much the same, your best estimate of the overall effect is what you get from the combined group and don't worry too much about that you have one subgroup here that looks like it is a little bit different.

I guess I have a little bit of trouble understanding why this was developed as a noninferiority question in the first place. Why do you want to prove you

have a new product that is no better than the product that you have already got. So that did seem a little--it was hard for me to understand that. But I think it is efficacious.

DR. HENDRIX: Dr. Strader.

DR. STRADER: I would like to echo some of those comments. I don't have any problem believing that this is efficacious as well. I am disturbed by the idea of pulling out little subgroups of the population in an attempt to try to show some differences.

I think, if this is done in good faith, that we don't expect that the populations are going to be any different with respect to their response, then we should leave the data pristine as it is as opposed to trying to pull things out and make conclusions based on subgroups of subgroups, et cetera.

With respect to the comment that was made about noninferiority, I think that is usually the case when you present something. Not all the time, but you want to show it is at least as good as what you have got out there before

you start to show that it is preferable or it is better.

So I don't have any problem with the way that this was set up.

DR. HENDRIX: Dr. Veltri.

DR. VELTRI: I was going to also comment on the drug-development side. Within the same class of drugs, you generally err on the side of noninferiority. If you are superior, that is great. So that is not unusual.

Now, if this was a new class, if you will, then one could argue, well, you could do noninferiority but you more likely want to do superiority. So that is not unusual from a drug-development perspective.

DR. HENDRIX: Dr. Freeman.

DR. FREEMAN: I guess--I mean, I think it is efficacious. And I think some of the data from some of those subgroups like looking at the MA-LRI and looking at the days of being in the ICU and the days of intubation all look promising.

This is just echoing what other people have said but I wonder if it was just--kind of the wrong question was

asked. Those questions came up about the Northern Hemisphere, the Southern Hemisphere, the U.S. versus other countries, ROW, in terms of are the U.S. people hospitalizing less.

I wonder if it was the wrong question because it is true, when you look at the actual data we have and that is when you start to think, okay, it is noninferior but we can't prove that it is superior with the adverse effects. I guess that is what is troubling me. Same as a lot of people.

DR. HENDRIX: Dr. Graham.

DR. GRAHAM: I was thinking about what we would say if mota was developed first and now we were comparing palivizumab to decide if we should replace motavizumab. You would be faced with the idea that you would have to give up--if palivizumab was looked at here as noninferior, it would look inferior. So you would have to give up a little bit of efficacy to have a few less side effects and it would be very hard to give up that level of efficacy even though the side effects were fewer.

So if mota was developed first and palivizumab was developed second, we would be thinking of this the other way around. So motavizumab would be a good thing to have if we had nothing else. I will leave it at that.

DR. HENDRIX: Dr. Clay.

DR. CLAY: I guess my question would be to the pediatricians here. Would you use palivizumab in Native Americans at high risk after you have seen this data?

DR. FREEMAN: I am a pediatric infectious-disease person, but I was thinking about that when someone else brought it up. Which patient are you going to use it in. Maybe it is a little more efficacious in certain--we don't have the statistics to back us up, but if we had more patients and some of those hospitalization data looked promising that maybe it would be a little bit better.

Then you would say, okay, well, maybe the sicker ones you can give it to. But then, someone else made the point, oh, so you would give it to the sicker ones and take the risk. But I think, at this point, I would be nervous to give it to the sicker ones because they are the ones that

could have--if there is a hypersensitivity reaction, they are the ones that could actually have more trouble from that hypersensitivity reaction.

I mean, I think the data that was shown with the hypersensitivity reactions, it didn't make it look that bad. I mean, none of them even got hospitalized. But, when you think about that in the grand scheme of things, if it was a sicker patient that they easily could have ended up hospitalized.

So, anyway, I am struggling with which patient I would choose. So I didn't really answer that.

DR. HENDRIX: Dr. Maldonado.

DR. MALDONADO: I do believe that this drug, all the way from the preclinical in vivo, in vitro and clinical data, does support efficacy. So I would say yes to the question.

I think the critical issue is is it more efficacious than the product that is currently available. I think there is a strong suggestion that it is. I think there are some issues that we have brought up today and have

been brought up by the FDA as well that I think cast some doubt as to the degree of that.

I also think that there are some issues around comparison of the original trials and the efficacy bounds, the confidence-interval bounds. And we went through that and I still feel uncomfortable with the way that was done and how we are accepting the current 50 percent treatment effect.

So I still feel that--hindsight is 20 20, but I think that piece of it makes me doubt that--or it makes me think of this as probably more efficacious than it looks at first blush.

On the other hand, coming back and, again, I can't separate Question 1 from Question 2. When I said cost/benefit, I guess I meant really benefit/risk or cost equalling risk rather than dollars because I do think--and we have had a number of other examples where a small signal premarketing turns into a much larger signal postmarketing. So that is a concern.

Again, it is a signal that drops out. But I

think, in this situation, the signal is worrisome. So your question about would we use this, I think it depends on what that safety signal really turns out to be in the bigger picture and which patients are at higher risk and whether or not those risks can be ameliorated by pretreatment or by selecting out for patients that--I mean, I am not a cardiologist. I don't know if kids who get steroids or other interventions are going to do better or worse if they are pre-treated or not. We have to see that data first.

So, in summary, I think it is efficacious. I think it is probably more efficacious than the data suggest for a number of statistical as well as clinical reasons. And then I think the safety issue plays into efficacy in terms of what populations would you use this in because we need to know better where does that balance out.

We need to know more about whether the safety balances out the risk here, the efficacy.

So I think the critical question, though, too, is, again, coming back to the safety issue, are these going to be answered on this side or that side of market and

licensure.

DR. CLAY: I was asking about palivizumab, not motavizumab in Native Americans but yet the other drug was--and so would you be comfortable using the drug currently on the market in Native American pre-term infants or those that you consider at high risk for that. That was my question, not the mota. Thank you.

DR. FREEMAN: I actually think for a healthy infant I don't think I would be--the Native American ones are--you know, they are not premature. They don't have the heart disease. I mean, I think I would feel fairly comfortable using either right now.

DR. MALDONADO: So the issue around those children has more to do with the cost of the product than it has to do with prevention of disease. So, yes.

DR. HENDRIX: I want to get back to the question. As fascinating as that was, I will let you all do that later. Dr. Ellenberg.

DR. ELLENBERG: Just to clarify my comment before about the noninferiority study. Yes; it is quite common to

have noninferiority studies when you put something on the market. But, typically, there would be some advantage that people would say; this is not more effective but it has some other advantage. Often it might be safer or it might be easier. It is a pill instead of an injection or an infusion. There is some advantage.

I wasn't here. These are very similar products and so that was sort of puzzling. What was the anticipated advantage if it wasn't going to be superior in efficacy? Was it anticipated that it was going to be safer? So that is sort of what confused me.

I would have liked to see, and I don't know whether anybody has done this--I have sort of been scribbling here on some kind of number-needed-to-treat kind of analysis where it looks like maybe this compared to this at best, there might be two in 100 reduction of all lower respiratory infections and maybe there are two in 100 increase in skin events and maybe a lower number, three in 1,000, maybe, of the high-level events.

I am not very trusting of these sort of scribbling

things that I am doing right now and it might have been nice to see more of an analysis like that that really tried to integrate the benefits and the risks.

DR. HENDRIX: Let me clarify something. Would you like an answer to your question or would you be happy considering your question about what was the anticipated benefit or whatever, why noninferiority. Would you like that answered?

DR. ELLENBERG: Yes; sure.

DR. HENDRIX: So there are a couple of people. So let's go ahead and ask the sponsor if you can answer that question.

DR. CILLA: Slide G43. Slide on.

[Slide.]

DR. LOSONSKY: So this is counting on the left the comparative advantage. So it is subtracting out or in differences we saw with palivizumab. And we were conservative here on the right where we counted not just those level 3 and SAE events but also any specific skin event within two days.

And it is a combined 110/124 data. So, for every 1,000 patients treated, we would expect six additional cases of these events. And for every 1,000 patients treated, we would expect to prevent 22 additional events that are combined lower respiratory-tract infections or hospitalizations.

And then 117 is the same data with obviously the comparator subtracted in or out is the placebo.

DR. ELLENBERG: Right. But I would point out that what you have done there is you selected your primary endpoint and then combined that with one of a number of secondary endpoints, the one that, in fact, had the strongest effect.

DR. LOSONSKY: We combined the relevant one for the activity of the drug because I think that is what the discussion is about an RSV effect.

DR. HAVENS: Did they do that for just hospitalization? Do you have the same data for just RSV-associated respiratory hospitalization, that combined MA-LRI with hospitalization? Do you have RSV--the primary

endpoint.

DR. HENDRIX: Which is what you asked for, but I think it is useful to see the isolated primary endpoint, the pre-specified.

DR. RALSTON: But you can do that. I did it before I came. It is a half of 1 percent and the number needed to treat is 200.

DR. LOSONSKY: So, slide on.

[Slide.]

Here it is with the different endpoints.

DR. HENDRIX: Thank you.

DR. LOSONSKY: So RSV hospitalization-MA-LRI combined and this has all skin events of interest and these are those that are specific.

DR. HENDRIX: So it all depends on how you--

DR. LOSONSKY: I should add that are we really talking about equivalent outcomes, though. So, when you have a skin event that you either treat or don't treat with a steroid or an antihistamine and it rapidly resolves, no sequelae, which is what the data we have now--that is the

evidence we have now compared with a lower-tract disease.

DR. HENDRIX: Okay. Thank you very much for providing that. So, just to summarize some of that, I think it points out the complexity of this and it all depends on whether you are going to lump or split and consider serious events or all events on the negative side. It is a complicated calculus.

So let's come back to the efficacy question in particular, because, in the third question, you are all going to do the calculus in your head and make a yes or no or an abstain. Then we will know what you think about any summary of the data.

So let's come back to any additional comments on the efficacy question. Dr. Roland.

DR. ROLAND: Well, I like that the discussion started with the placebo-controlled trial and it is obvious that there is efficacy with this drug.

But I thought that Dr. Ellenberg asked a different question that didn't get answered. It is actually the same question I asked you guys in the beginning which is I am

confused about why the sponsor would design a noninferiority study unless there was some other non-efficacy advantage.

So you had a product on the market that had bad side effects; you thought this one would have fewer side effects. You had a product that was harder to use; you thought this one would be easier to use.

So my understanding of the presentation is, well, if it is noninferior, we have a chance. If it is superior, it is great. Let's power it for noninferiority. If we see it is superior, that is great.

But now we are struggling with--

DR. HENDRIX: Right. Let me just comment on that and then--which begs the question about what--and that is why I asked the question about the long-term plans for pali because their intent, by the design, appears, at least, to replace their own product which has its own obvious advantages.

But, otherwise, I agree with both of you and the others that have raised this is it is difficult to understand why they wouldn't look for the specific niche or

make that clear in the design in terms of the subject selection or other elements in terms of the stratification a priori in these studies to answer that question.

So I think that remains unanswered.

Dr. Hagedorn.

DR. HAGEDORN: Well, you are touching on the concern that I have. I guess I will ask it more as a question. So, regarding the efficacy, I think that mota--it is clear that mota does have an effect but I think no one can state at this time that it is more effective than pali. If its relative advantage and its niche regarding use, clinical use, were to be determined in a phase 4 type study, what are the possibilities that you then lose pali and now you have a drug that you still haven't completely measured all its adverse events.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: And then I think we have, for the most part, discussed the need for more data and whether or not this should be postmarketing. I wonder if this question is for us or for the FDA, but it seems that these patients that

have had these hypersensitivity reactions required intervention. Whether or not they required hospitalization, it doesn't seem like is the case. But they required pharmacologic intervention.

So I just wonder if this does go to label whether it would be mandated that there is a time period in which these patients are observed after administration and whether or not that could be something that we would do.

DR. HENDRIX: So you will get a chance to comment on that in the third part.

DR. ZUPPA: I'm sorry.

DR. HENDRIX: Because when you make your decision, yes, no, or whatever, you are also going to be asked to specify conditions either premarketing or postmarketing depending on how you voted. So we can come back to that.

DR. ZUPPA: Thank you.

Dr. Atkinson.

DR. ATKINSON: I am not sure whether I am stepping outside the bounds of the question right now but I was just going to say, well, if postmarketing studies showed that it

was 10 percent more effective than pali in reducing hospitalizations, which I don't think is excluded by the data that we have seen today, then it would be cost-effective for 3 or 4 per thousand non-life-threatening skin reactions and maybe a rarer case of more severe anaphylaxis might be an acceptable risk in this high-risk population that comes in and not infrequently expires from RSV.

DR. HENDRIX: Okay. Let me summarize Question No. 2. I think there was a very consistent consensus about the demonstration of efficacy of motavizumab. There was a bit of back-and-forth about whether there was evidence for it being better. There was anticipation that might be the case but there were a number of opinions stated that there was not demonstrated evidence that it was superior.

There were questions raised by a number about the reason for a noninferiority design that would preclude the ability--or to have underpowered this to be able to show superiority.

The question about the role of the subset analyses, and I think some of the useful roles for that

might be helpful in selecting the niche that could be part of the package insert or to direct future studies premarketing, and also to identify what population this drug would best be used in where there would be an appropriate balance of risks and benefits.

Finally, the comment about the benefit of larger studies to answer some of these questions to pick up sort of the niches and superiority issues that remain to be sorted out.

So we will go on to the third question. I will state the question and then I am going to read some text so you all understand how this is going to work. No. 3 is, given the potential benefits and risks, should motavizumab be licensed for marketing.

We are going to vote on this and, in fact, let me just clarify. Do we discuss first or just vote and then we discuss afterward? Discuss first and then vote? Okay.

So I will open it for discussion first and then I will go through the details about how the voting is going to work. I will say that, after the vote, we will all have a

chance because we are going to go around and, for the record, state how you voted, although that will be done simultaneously privately with the electronic system.

Then you will be able to make a comment specifically on the two questions that follow that.

So I will go ahead and open this, then, to panel discussion. Again, the same comment about the comments from the public observers and attendees.

Dr. Havens.

DR. HAVENS: So it would help me understand sort of how to vote here to get a feeling for the premarketing and postmarketing control that might be available to put on the company. If you are in the camp like I am that considers mota to be a kind of an exciting drug that might really be more beneficial if studied in the sickest population, the question is, are we better off saying, don't allow it to be marketed yet but do the study first, or is the power of the FDA over the company to get the studies done equivalent whenever we say it is okay to get marketed?

DR. HENDRIX: Dr. Birnkrant, do you want to

answer? My understanding of this is essentially you--assume that you have the power of the FDA and your issues are, in a way, before you. If no, if your belief is that it is no, then you decide what additional studies are required to get to yes.

And if you think yes is there, are there restrictions that ought to be applied to that and postmarketing studies that should be done.

I think that is what they want to hear. If it is not enough, what is enough? If it is enough but there are restrictions or additional studies you will want, what would those be? Is that fair?

DR. HAVENS: Well, I guess--

DR. HENDRIX: I'm sorry. I was actually asking the FDA--

DR. HAVENS: Well, no, but it kind of depends on what your definition--

DR. HENDRIX: --if I was consistent with their intention with the question.

DR. BIRNKRANT: That appears fair.

DR. HENDRIX: Thank you.

DR. HAVENS: But then the response is what do you mean by "enough," I guess.

DR. HENDRIX: That is up to you.

DR. HAVENS: Oh, god.

DR. HENDRIX: That is why you are paid the big bucks to be here, Peter. Let me qualify that. Give us a response generously more reasoned than the big bucks you are being paid to be here. I will put it that way. I don't know if everybody got that. It was too oblique.

I shut him up. I can't believe--okay. Dr. Graham.

DR. GRAHAM: I was going to just start by saying I think the problem that we are dealing with is that, if there is a benefit to motavizumab of reducing some of the severe diseases, is that better than having a few more, or dealing with a few more, skin rashes.

So the problem is there hasn't been a large enough study to see the extreme of hypersensitivity response and there hasn't been an extreme enough study in terms of

sickness of the subjects to see--if you really did 100,000 subjects, would you see death from anaphylaxis.

If you really did extremely sick subjects, would you see prevention of death from RSV? So we are dealing with this decision about skin disease versus respiratory-syncytial-virus-induced lung disease neither of which are lethal in the data that we have and so the extremes are not there for us to make easy judgements about.

So I would like to see either studies, as you said, in much sicker subjects or in a more selected population to see if you really could show that motavizumab was better than palivizumab in terms of reducing the extremes of disease, of preventing death and preventing some of the extreme disease symptoms.

DR. HAVENS: But then the question is--right. Understanding that that is what you might want to see, do you vote no to approve until we have that? Or would you say, well, it is okay to approve but just do those studies after it is approved. That is kind of what I am trying to get a feeling for.

And I am willing to make a personal decision in the privacy of my own brain, but I am just interested in hearing how that equation goes.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: I guess what I see is that this drug is possibly better than what we have now. We don't know that. I feel like it is effective but I don't know that it is better. But we do know that it has a risk that the other one doesn't seem to have because those data seem pretty compelling.

So we have a potential on one hand and a definite on the other in weighing that.

One question I have though is the risk of having a hypersensitivity reaction was clearly much higher in those who had the antibodies. But, while that accounted for a minority of the hypersensitivity reactions, you clearly did have a subgroup that was at much higher risk.

So a question is how feasible would it be to evaluate people for this before giving them--I mean, is it possible to identify those children so that they would say

you would not give the drug to them?

DR. HENDRIX: Dr. Maldonado.

DR. MALDONADO: So some of the conversation is a little bit duplicative from the previous questions, but I really think, at this point--I really don't think we are going to be able to get these answers postmarketing. Look; I am thinking about the clinician who is already struggling to get their five doses in and the Red Book Guidelines are so hard to read right now that you have to--they have put out an errata. They actually made a mistake in trying to make the table look reasonable.

It is very hard. You have to use date of birth and you calculate number of doses and how old the baby was and how high the risk is. So it is a very complex issue right now, even with a product that we know works well.

Again, there is a lot of promise here but I think trying to decide at this point what studies are to be done postmarketing are--I don't think there are any guarantees that they would be done the way they would need to be done to answer the question.

So I think there are going to be some specific questions that will need to be answered. In particular, I think the issue will have to be--this issue of the sicker kids is a really critical one. I also think that, if you want to generalize the data to this outpatient--this is a novel concept.

Unfortunately, the pivotal study that was done for licensure of the pali was just not comparable. You can't really look at that as--I am convinced that those patients were too different from the patients that we are seeing now. I realize that it is a moving target, but that is very old data and I think that the population at risk now is very different.

Although I feel like it is lining up pretty well, I just don't think it is ready for prime time at this point unless those higher-risk patients are on line and we know a little bit more about what happened on the outpatient side.

DR. HENDRIX: Dr. Roland.

DR. ROLAND: I guess I am concerned that this is the only chance that we have premarketing to answer the

unanswered questions about superiority and to have more experience around adverse events.

I keep thinking through my own clinical practice when it is I have a couple of choices and it is important to have a couple of choices, and I can't see the analogy here with these two drugs. Plus, I think we understand that there will only be one choice in some period of time if this drug is approved.

But I am struggling, if we were to make that recommendation, with how the sponsor would be able to design a study that takes into account clinician practice and how confounding and difficult that was. That is not straightforward to me.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: Just a couple of things that I am thinking about trying to make this decision is, so if mota is approved, does pali go away, so is there still a choice. And then, if we go to approve it, what I alluded to earlier, whether or not there will be restrictions on the time that a child would need to be monitored post-

administration and whether or not it would be approved for the study population, the population that was actually studied, as opposed to all-comers, so whether or not it would be approved for children who were not mechanically ventilated or sicker.

But I am pretty much in agreement in that I think that now is the opportunity to have these questions answered prior to licensing.

DR. HENDRIX: Dr. Strader.

DR. STRADER: I am struggling with the difficult task of answering the question that is asked directly as opposed to wondering what might happen in the future or in the past.

The question says, given the potential benefits and risks, should it be licensed for marketing. So I will try to answer that question, my opinion. I think, given the benefits that show that this drug has a greater affinity for binding to the F protein of RSV in vitro, given the efficacy data that they showed us based on a study that was supposed to look at noninferiority--not in superiority but just

looking at a drug that was not inferior to the one that is there, they have met their stated objectives. They have shown what they intended to show.

There are increased hypersensitivity reactions. Not being a pediatrician, I don't know if that means that a child who has significantly hemodynamic congestive or coronary heart disease is going to get into serious trouble if they get an urticarial reaction and die as a result of that, or be hospitalized longer.

But I think that these things we can find out in post hoc analysis. We can look at patients with more severe disease. I was under the impression that the patients that were included with hemodynamically significant disease were seriously ill. But it appears to me that the pediatricians here don't think they were.

So I think that those kinds of things can be done with very close monitoring of particularly patients that pediatricians would consider really seriously ill.

The other issue that I think could be done postmarketing is to see is there any way of preventing these

reactions from happening. Can you give Tylenol and Benadryl or something pre-dosing to prevent some of these reactions from happening in children which may allay some fears with respect to whether or not these grade 2 and grade 3 reactions that were seen can be prevented.

So I think that they met the burden that they were trying to show and that there certainly is more that needs to be done, and I am sure that pediatricians could probably come up with some better ideas as to how to follow this forward.

But I don't know that the question of the few what I consider non-life-threatening skin reactions from a hepatologist point of view should prevent the approval of a drug that appears to be very efficacious.

DR. HENDRIX: Okay. I think we are there. I'm sorry; Dr. Maldonado.

DR. MALDONADO: Actually, just to follow up. Obviously, the safety issues are important but, actually, even without the safety issues, I still think that there are some comparator issues about the two products.

So I didn't even take that into account in terms of that. So the safety is obviously important, but you have to put safety in the context of how much are you gaining based on the safety.

So, if you gain something from this product, then the safety is not a big issue. But if they are equivalent and this one is less safe--so, again, the safety issue, I think, is distinct from the efficacy issue which is why I think they gave us two different questions.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: I am just trying to look at it from a practical perspective. I am in the ICU and I am rounding and there is a family and I say, you know, I want to do some RSV prophylaxis. And the mom or the dad says, well, why did you pick--you know, what are my choices.

And I say, well, there are these two drugs. I don't know if one works better than the other but one of them has a slightly higher risk profile, although that is not really clear either.

Just from a practical perspective, and I am trying

to treat these families in full disclosure, what are you really going to do?

DR. FREEMAN: I just want to say I totally agree with that. I think that is the problem with the conversation. I think we all feel like there is a trend--at least, I feel like there is a trend that it can be more effective. But you can't say right now--you really can't say, look, it is significantly better.

But this one--I would probably recommend that they are watched there for four hours or something for the newer one. But I think that is the problem when you talk to the family.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: Just to comment on further studies, I think--although I don't disregard the Southern Hemisphere data for the current analysis, I would say that, for further studies going forward, we probably would want to see them U.S. or North-American focused just to reassure us about that issue.

DR. HENDRIX: So now I think we are there. Let me

describe--we are going to vote on this question yes, no or abstain. So we will be using this new electronic voting system for the meeting. Each voting member--look at your microphone. Each of you has--and they are now flashing at you. This is where your heartbeat goes up quite a bit, actually.

So there are three voting buttons on the microphone, yes, no and abstain. Once we begin the vote, please press the button that corresponds to your vote. You will have approximately 20 seconds to vote.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. I will read the vote from the screen into the record. Next we will go around the room and each individual who voted will state their name and vote into the record as well as the reason why they voted as they did.

Now, let me just ask, are there any questions about how this is going to work because, once we start, you have got 20 seconds to get it done. This is the time to take some deep breaths.

DR. CARGILL: Or a beta-blocker.

DR. HENDRIX: Right; or a beta-blocker. I won't necessarily endorse that. So we are set to begin. If there is no further discussion on the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote.

[Electronic voting.]

MR. TRAN: Please press firmly on your choice. If you are unsure, you can press it again. You only get one vote. Don't worry.

There is one person that did not get into the system, so could you please re-enter your vote. Press firmly.

DR. HENDRIX: The results, for the record. Yes, there were 3. No, there were 14. Abstain, there were 0.

So, at this point, we are going to go around the room. We are going to start with Dr. Murata.

DR. MURATA: I had voted yes with the following two qualifying comments. I understand the limitations that

were laid out by the agency during the opening comments that this is an ongoing review process of the product for licensure.

Two, I make these comments as a person who does RSV bench and translation research and also has embarked upon some collaborative peds ID-related RSV projects.

So, from my perspective, post-palivizumab era, there appears to be a trend towards decreased hospitalization for RSV in general. And that is probably reflected in some of the comments by the sponsor about the MA-LRI as being one of the endpoints in the current licensure studies and not for the palivizumab. These nuances have probably affected study design and interpretation.

The limitations of the diagnostic and geographic data are noted. But, in my personal opinion, it appears that it is efficacious with respect to--over palivizumab regarding the MA-LRI in Studies 100 and 124. And this likely outweighs the safety issues for the rash.

So, for the postmarketing studies, I had three

thoughts. One is the prospective patient population studies that were suggested by other members of the committee, voting committee, including CHD pre-term on ICU and incubator or the severity of illness and its effect on motavizumab therapy.

Two, as outlined in the sponsor's Slide 67, in principle, I support the notion of the prospective surveillance study but also paying particular attention to the ADA titers and their presence and their relationship to skin and all AEs. And also the retrospective cohort study.

Both types of studies should, in my opinion, focus specifically on certain factors that were discussed during this meeting including geographics and viral subtypes and resistance.

DR. HENDRIX: Dr. Zuppa.

DR. ZUPPA: I voted no. Do I need to state my name?

DR. HENDRIX: No. My stating your name is enough. Thank you.

DR. ZUPPA: For much of the reasons that were

already discussed, especially, for me, I think it needs to be studied in a sicker population of chronic lung disease. I feel that this is a population that would problem benefit from it most and we don't know what the adverse-event profile will look like in that population.

DR. HENDRIX: Dr. Atkinson.

DR. ATKINSON: I voted no. I guess what convinced me was the notion that I am convinced that there are increased risk factors to giving this medication and it is not clear to me that it is more efficacious than the drug that we already have.

So it just seemed to me that we need more information to resolve these two issues. It could very well be a worthwhile trade, as I mentioned earlier, but I am not convinced that we have enough data to make a firm decision at this point.

DR. HENDRIX: Dr. Maldonado.

DR. MALDONADO: I voted no. Although I do believe that this drug did show evidence of efficacy, I think the comparator drug--I didn't see enough differences between

that and the comparator drug at this point to feel like this would be an easy decision for a practicing clinician to make a decision or to have--even if this were the only drug available to have this as the only option given what we know about the current relative risks of illness and breakthrough disease in this population.

I also secondarily think that better definition of the safety profile would be really helpful for the clinician.

DR. HENDRIX: Dr. Luque.

DR. LUQUE: I voted no. Similar to the others, I am not convinced that this product has an advantage in terms of efficacy compared to the current marketed product. But it does seem to have an increase in adverse events which is very concerning.

I think we need larger studies and, in particular, we need a more homogenous type of cohort and, particularly when it comes to the demographics, to avoid this issue of different demographics perhaps influencing the results.

I also think that, for those subjects that had

adverse events that were not necessarily linked to the anti-drug antibodies, there need to be more detailed studies in terms of IgE or any other immunological studies to try to pinpoint the cause so that we are more comfortable as to what we are dealing with.

DR. HENDRIX: Dr. Cargill.

DR. CARGILL: This is a difficult vote but I did vote no. I do think that there is tremendous potential with this agent. However, I think there are several things that are concerning.

I agree with the comments and would amplify upon them further particularly based upon the question which had to do with "maximize the use." I am not convinced that we have the data that would be able to allow people to advise them in a way that they could prioritize or maximize the use.

While we see on the sponsor's Slides 31 and 32 this suggestion of efficacy and, certainly again on 39, I think there are enough other questions including and not limiting to that this is a panel that is supposed to be

approving agents for U.S. use, that we need more U.S. studies.

In addition, to that, if we were going to try to further delineate these safety issues, that we don't have sufficient data and we would need to know more. The ADA was only helpful in some of the patients who had side effects and not in all. If we are going to advise people on the best way to use this, we need to explore this further.

I think these things mean that this is an opportunity to get the signal straight now as opposed to post hoc.

DR. HENDRIX: Craig Hendrix. I voted no. I think the primary reason a lot had to do with the comments from a lot of the practitioners on the committee that made comments about they wouldn't know exactly how they should be using this drug. It was that kind of ambiguity that, for me, was tipping beyond the point of ambivalence.

Initially, I was struggling with balancing the clear noninferiority and the efficacy that, for me, was not in question with the risks that seem that they could be

managed as they were on the study.

But the questions would be, in larger numbers, would it be clearer how to use this drug. If there was data in sicker patients and in a larger group of patients, there would be both more information for how to use the drug and more information about the riskiness and whether or not these relatively small number of events, some of which were very important, were more serious than that.

So I think larger numbers will help in both directions to understand the niche for this drug in the same marketplace as another drug that already is very effective and also to understand the risks so that these could be managed balancing the risks against the benefits.

Dr. Clay.

DR. CLAY: I voted no. In terms of additional studies that I would recommend to the sponsor; doing some genetic exploration as to what patients might be most predisposed to developing hypersensitivity reaction and also to take this product into development to the extent where you would be able to find out the advantages and the utility

of this product in the clinical setting, whether it be a decreased dosing, alternative dosing, route.

I don't know that you would really be able to ever change this side-effect profile, but perhaps being able to identify those most predisposed to the hypersensitivity would be a benefit in conjunction with improved dosing would, I think, then, with your efficacy being nearly what it is for your currently marketed product, that would, then, make me feel much more comfortable about bringing this to market.

DR. HENDRIX: Ms. Walden.

MS. WALDEN: I voted yes based on the prospect of the benefit of improved prophylaxis especially after having dealt with the effects of repeated RSV infections with my own baby. Those effects are lasting and those effects made her a lot sicker for a lot longer. So the prospect of a better prophylaxis was my primary reason for voting yes.

And I also wanted to give, or felt like giving, physicians the choice between the two drugs and making the clinical decision as to whether or not the particular child

in question would be a good candidate for that particular drug.

DR. HENDRIX: Dr. Ellenberg.

DR. ELLENBERG: I voted no. I think that there are lots of reasons to hope that this drug may be better, but it did not meet the bar of showing that it was better. I am sure that these results disappointed the sponsor. I am sure the sponsor expected from the early promise of these data that they would be able to show this drug was better than what was there.

But that has not been demonstrated and, in the light of a drug that may be as good, and then we have these other concerns about comparisons with the previous study and some other issues together with a clearly potentially serious new reaction, that that led me to vote no.

DR. HENDRIX: Dr. Freeman.

DR. FREEMAN: I voted no for a lot of the reasons that have already been stated. I think this drug will turn out to--I think it has tremendous potential. I think it will find its niche. I think a lot of the trouble was, in

terms of--you know, the hard problem I had was should it be a postmarketing analysis then looking into the real effect of these adverse effects and the real efficacy.

But this is a particularly fragile, vulnerable population and I was worried that it wouldn't be done in quite as controlled a setting. So I thought this was a good opportunity for that.

I also think the role of the ADAs isn't clear, how much effect that is having with the hypersensitivity reactions. That would be interesting to explore more. And just doing more focus on trying to make the superiority analyses and some of the indices like the days of hospitalization and ventilation. Then you would be much more willing to accept the risks.

DR. HENDRIX: Dr. Roland.

DR. ROLAND: I also voted no. I was very ambivalent throughout the entire reading of the materials and the discussion. I found the discussion also to be extremely helpful. I think what it came down to is just listening to myself, what I kept saying throughout. I still

am not comfortable with whatever the rationale was for the noninferiority design and, unfortunately, the data left me with two big areas of uncertainty.

One is what is the relative efficacy of these two drugs and the other is what is the real potential for serious adverse events. I think there is so much that we do in clinical medicine in the absence of data and we all bemoan that, and we would never have the data if the drug was approved.

So I kind of felt like there was no choice although it was difficult.

DR. HENDRIX: Dr. Graham.

DR. GRAHAM: I voted no. I think that, in doing the inferiority-noninferiority test that the hope would be that, in postmarketing, you could show that it did have additional benefits of either transmission to the next person--the idea that it is blocking the antigen drug suggests that it might also block the transmission to the next person.

But I don't think you can show those kinds of

effects until studies get very large. But the fact that the hypersensitivity came up in the middle of looking at noninferiority makes you feel like superiority, now, is needed. And I think superiority could be shown.

So I would like to see superiority shown and then, in postmarketing studies, get very large studies, to show that the risk/benefit ratio, then, is reasonable postmarketing if superiority can be shown in some way to justify the larger postmarketing studies.

DR. HENDRIX: Dr. Ralston.

DR. RALSTON: I voted no for the reasons previously stated and I don't think I have anything else to add to the discussion.

DR. HENDRIX: Dr. Havens.

DR. HAVENS: Peter Havens. I voted no and have nothing to offer except potentially thinking about an outcome that is actually a measure of physiology and degree of severity rather than just physician-derived, like hospitalized or not, might allow you to show a difference in a smaller number if further studies go forward.

DR. HENDRIX: Dr. Strader.

DR. STRADER: I voted yes. I think that the sponsor showed that the drug was at least noninferior and, in some cases, more efficacious than the one we have available. I was somewhat troubled by the hypersensitivity reactions but I thought they could be treated, as the sponsor showed, and there were no life-threatening reactions.

I thought that the drug could be marketed to treat children with moderate disease and that further studies could be done in children with more severe disease postmarketing to answer all the questions that were presented here during the panel today.

DR. HENDRIX: Dr. Hagedorn.

DR. HAGEDORN: I voted no. My concern was basically adverse events and what was the potential advantage of this agent of what has been currently used in feeling that it should be shown at least in one setting that it has some advantage.

I really don't have anything more to add than what

has been said.

DR. HENDRIX: I am just going to give a summary of this point. There was a lot of stated ambivalence and difficulty with the decision first of all. There were difference of opinions about whether or not the questions--there was consensus of questions that needed to be answered. It wasn't a clear consensus about whether they could be answered premarketing or postmarketing and whether one would be better than the other.

It also seemed that it might have been pivoted on that issue within each of those on the committee to make their decision yes or no because I think a lot of the other points weren't really controverted.

The recommendations for postmarketing, in fact, were similar to the recommendations for premarketing for reasons I said, perhaps, that, in postmarketing, more detail is needed on the patient populations to sort out which patient populations in which it might be used and that the package insert might be crafted in a way that the limitations could be--the limitations of the risk and the

hypersensitivity could be managed appropriately.

The premarketing concerns in those that voted no was to look at sicker, larger groups to define the role of the drug and its niche if it were not demonstrated to be superior or if it could be demonstrated to be superior. that would be helpful, and also to better define the risk frequency and the severity and the possibility for progression to more serious side effects once larger numbers are exposed.

I will leave it at that to summarize.

The last word, then, comes from the division, if you have any comments you would like to make. Dr. Birnkrant?

DR. BIRNKRANT. No. Thank you. I thought that the discussion was quite helpful. I think we have a lot of good information with regard to what additional studies we need to be able to better assess this drug with its risks and benefits in perhaps a more ill population.

We appreciate the contributions of all the members of the panel today and we found the meeting quite helpful.

I want to thank everyone very much.

DR. HENDRIX: Thank you all very much for your contributions. We are adjourned.

[At 4:04 p.m., the meeting was adjourned.]

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